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SCHOLARLY REVIEW

Evidence-Based Supplements for the Enhancement of Athletic Performance

Peter Peeling and Martyn J. Binnie
The University of Western Australia and Western Australian Institute of Sport

Paul S.R. Goods
Western Australian Institute of Sport

Marc Sim
Edith Cowan University

Louise M. Burke
Australian Institute of Sport and Australian Catholic University

A strong foundation in physical conditioning and sport-specific experience, in addition to a bespoke and periodized training and nutrition program, are essential for athlete development. Once these underpinning factors are accounted for, and the athlete reaches a training maturity and competition level where marginal gains determine success, a role may exist for the use of evidence-based performance supplements. However, it is important that any decisions surrounding performance supplements are made in consideration of robust information that suggests the use of a product is safe, legal, and effective. The following review focuses on the current evidence-base for a number of common (and emerging) performance supplements used in sport. The supplements discussed here are separated into three categories based on the level of evidence supporting their use for enhancing sports performance: (1) established (caffeine, creatine, nitrate, beta-alanine, bicarbonate); (2) equivocal (citrate, phosphate, carnitine); and (3) developing. Within each section, the relevant performance type, the potential mechanisms of action, and the most common protocols used in the supplement dosing schedule are summarized.

Keywords: athlete performance, ergogenic aids, nutritional intervention

Numerous factors contribute to peak athletic performance. Among these, a strong foundation in physical conditioning and sport-specific experience, in addition to a bespoke and periodized training and nutrition program, the latter based predominately from whole food choices, are essential. Once these underpinning factors are accounted for, and the athlete reaches a training maturity and competition level where marginal gains determine success, a role may exist for the use of evidence-based performance supplements. Although an array of supplements are marketed for the enhancement of sports performance, many lack robust evidence of an ergogenic benefit. Furthermore, some may actually impair performance, often due to gastrointestinal (GI) concerns, while others are potentially detrimental to an athlete's health. Finally, numerous ingredients in commercial supplements, sometimes presenting as contaminants or undeclared ingredients, carry a risk of inadvertent anti-doping rule violations (Baylis et al., 2001). With this in mind, athletes and their associated support teams should only consider performance supplements where a strong body of evidence supports their use as safe, legal, and effective.

The following review focuses on the available evidence base for performance supplements that are commonly used in sport, summarizing the type of event/exercise scenario they are suited to, the potential mechanisms of beneficial effects, and the typical dosing schedule/protocols of use. The supplements of interest have been divided into three categories according to the strength of evidence supporting their use for the enhancement of sports performance. These categories include: (1) established, (2) equivocal, and (3) developing performance supplements.

Established Performance Supplements

There is robust evidence that the following supplements can enhance sports performance when used according to established protocols.

Caffeine

Caffeine, a stimulant that is ubiquitously consumed in the diets of most adults, has well-established benefits for athletic performance.

Peeling and Binnie are with the School of Human Sciences (Exercise and Sport Science), The University of Western Australia, Crawley, Western Australia, Australia. Peeling, Binnie, and Goods are with the Western Australian Institute of Sport, Mount Claremont, Western Australia, Australia. Sim is with the School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia. Burke is with the Australian Institute of Sport, Bruce, Australia; and with the Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia. Address author correspondence to Peter Peeling at peter.peeling@uwa.edu.au.

The mechanisms underpinning these benefits include adenosine receptor antagonism, increased endorphin release, enhanced neuromuscular function, improved vigilance and alertness, and a reduced perception of exertion during exercise (for review, see Burke, 2008; Goldstein et al., 2010; Spriet, 2014). There exists a lengthy research history on caffeine supplementation across a range of performance protocols, including endurance-based situations, resistance training exercise, short-term supramaximal efforts, and/or repeat-sprint tasks. Of note, recent interest in this area includes investigation into the efficacy of lower caffeine doses, variations in the timing of intake before and/or during exercise, and the lack of need to include a withdrawal period for performance effect optimization (Burke, 2008).

Endurance performance. Caffeine supplementation is known to improve endurance capacity during time to fatigue exercise tasks—for instance, during activities such as treadmill running to exhaustion (French et al., 1991) and resistance training exercise repetitions to failure (Duncan et al., 2013). Furthermore, ergogenic benefits are also widely reported during competitive situations, such as real or laboratory-simulated time-trial (TT) activities. A systematic review by Ganio et al. (2009) of 33 trials (representing 21 studies) found that caffeine supplementation achieved an average performance benefit of ~3.2% (±4.3%) when provided before and/or during endurance-based TT activities of varying duration (5–150 min), across numerous exercise modalities (i.e., cycling, running, rowing, cross-country skiing, and swimming). Studies reporting benefits typically used caffeine dosages of 3–6 mg/kg of body mass (BM), in the form of anhydrous caffeine (i.e., pill or powder form), consumed ~60 min prior to exercise (Ganio et al., 2009). However, there is also a growing body of work investigating the use of lower caffeine doses (<3 mg/kg BM, ~200 mg), provided both before and during exercise, which also reports an ergogenic benefit (Spriet, 2014). Of note, larger caffeine doses (≥9 mg/kg BM) do not appear to increase the benefit to performance (Bruce et al., 2000). In fact, such doses are likely to increase the risk of negative side effects, such as nausea, anxiousness, insomnia, and restlessness (Burke, 2008)—outcomes that would clearly negate any performance-enhancing outcomes. Interestingly, similar performance outcomes are expected in both habituated caffeine users and nonusers (Goldstein et al., 2010), with recent research reporting that high habitual daily caffeine intake (defined as 351 ± 139 mg/day) was associated with equivalent absolute and relative performance benefits as seen in low and moderate daily caffeine consumers (Gonçalves et al., 2017).

Low doses of caffeine consumed *during* endurance exercise have also been shown to enhance performance. In fact, 100–200 mg (1.5–2.9 mg/kg BM) of caffeine consumed in combination with a carbohydrate electrolyte solution after 80 min of a preload cycling task was shown to result in a ~4–7% improvement during a subsequent TT completed in ~26–28 min (Talanian & Spriet, 2016). Furthermore, 200–300 mg of caffeine administered in chewing gum form at the 10-km point of a 30-km cycling TT was shown to improve mean power output (+3.8%) during the final 10 km of the task, in addition to a 4% increase in peak sprint power output at the end of the task (Paton et al., 2015). In summary, caffeine supplementation provided both before and/or during endurance-based TT activities is likely to achieve positive performance outcomes.

Short-term, supramaximal, and repeated sprint tasks. The effects of caffeine on short-term, supramaximal, and repeated sprint tasks have been less well studied. Nevertheless, a systematic review of caffeine ingestion and high-intensity efforts of ≤5 min duration reported that ~65% of studies resulted in performance benefits, with a mean task improvement of ~6.5% (±5.5%; Astorino & Roberson, 2010). Specific protocols involving anaerobic activities include the study of a 1-km cycling TT, where caffeine ingestion (5 mg/kg BM consumed 60 min preexercise) was associated with a 3.1% improvement in task completion time, and a 3.1% and 8.1% improvement in mean and peak power output, respectively (Wiles et al., 2006). Such performance benefits have also been realized during short-duration maximal dynamic resistance training exercise, where measures of muscle torque production were significantly improved after the consumption of 6 mg/kg caffeine in the 60 min prior to exercise (Duncan et al., 2014). Furthermore, low caffeine doses administered in chewing-gum form (100 mg chewed for 5 min immediately preexercise) were shown to increase the distance thrown (+6%) by well-trained collegiate shot putters (Bellar et al., 2012). With respect to simulations of team sport activity, caffeine ingestion (6 mg/kg BM, 50 min before warm-up) improved total work performed during the first (+8.5%) and second half (+7.6%) of a 2 × 36 min repeat-sprint protocol in moderately-trained team sport athletes (Schneiker et al., 2006). Furthermore, a 1% improvement in mean sprint time was shown, when 300 mg caffeine was provided 60 min prior to a rugby-specific repeated sprint test in semiprofessional rugby-league players (Wellington et al., 2017).

In summary, low to moderate doses of caffeine (~3–6 mg/kg BM), consumed 60 min preexercise, appear to have the most consistent positive outcomes on sports performance in research situations, although a variety of other protocols (as mentioned above) also appear beneficial, and are practiced in real-life. Of note, athletes who intend to use caffeine as a performance aid should trial their strategies during training or minor competitions, in order to fine-tune a protocol that achieves benefits with minimal side effects.

Creatine

Creatine is another widely-researched supplement, with creatine monohydrate (CM) being the most common form used to supplement dietary intake from meats. When taken according to established loading and/or maintenance protocols, creatine supplementation can increase intramuscular creatine stores by ~30% (Harris et al., 1992), with the magnitude of response being inversely related to the starting concentration (Volek & Rawson, 2004). Within the muscle, creatine-kinase mediates the phosphorylation of creatine to phosphocreatine (PCr), a key substrate for high-intensity muscle force generation (Greenhaff et al., 1993). Whereas PCr levels decrease during high-intensity exercise to rapidly resynthesize adenosine triphosphate (ATP) from adenosine diphosphate (ADP; Rawson & Persky, 2007), elevated creatine stores allow a greater rate of PCr resynthesis, enhancing short-term, high-intensity exercise (Buford et al., 2007), particularly by enhancing the capacity to perform repeated bouts of effort.

Numerous reviews of CM supplementation identify performance benefits in single (+1–5%) and repeated bouts (+5–15%) of high-intensity exercise of <150 s in duration, with the most pronounced effects being seen during tasks of <30 s (Branch, 2003; Lanhers et al., 2017). As a result, creatine loading can acutely enhance the performance of sports involving repeated high-intensity exercise (e.g., team sports), as well as the chronic outcomes of training programs based on these characteristics (e.g., resistance or interval training), leading to greater gains in lean mass and muscular strength and power (Rawson & Persky, 2007;

Volek & Rawson, 2004). There is additional, albeit equivocal, evidence of changes in cellular signaling, metabolism, and water storage associated with creatine supplementation with potential flow-on effects such as enhancements of protein synthesis, glycogen storage, and thermoregulation (for review, see Cooper et al., 2012; Kreider et al., 2017). Therefore, there may be less well-recognized benefits of creatine supplementation for endurance sport athletes. In fact, recent evidence has shown that a combination of creatine (20 g/day for 5 days + 3 g/day for 9 days) and carbohydrate (CHO, 6–12 g/kg/day) loading may result in an increased power output during repeated high-intensity sprint efforts undertaken during the late stages of prolonged (>3 hr) simulated TT cycling, possibly reflecting the physiological demands of a late-stage breakaway during endurance events (Tomcik et al., 2018). However, CM supplementation is frequently reported to result in a 1–2 kg increase to body mass after the "loading-phase", likely a result of water retention (Buford et al., 2007), which may, in fact, be counteractive for the performance of endurance and/or other weight-sensitive sports, and should therefore be considered when choosing to use this supplement.

A recent meta-analysis of the most common and effective strategies for CM supplementation determined that a "loading-phase" of 20.9 ± 4.5 g/day (divided into four equal 5-g doses per day), for 5–7 days was reported across >80% of CM studies (Lanhers et al., 2017). Subsequently, a "maintenance-phase", typically involving a single 3–5-g CM dose per day, should follow the "loading phase" for the duration of the supplementation period. Such protocols have been established primarily from early work investigating muscle creatine loading in males (Hultman et al., 1996). Interestingly, concurrent consumption of CM with a mixed protein/carbohydrate source (~50 g of protein and carbohydrate) appears to enhance muscle creatine uptake via an insulin-mediated effect (Steenge et al., 2000), suggesting that creatine doses are best taken with a meal (or separate food supplement). No negative health effects have been reported with the long-term use of CM (up to 4 years) when appropriate loading protocols are followed (Schilling et al., 2001). In fact, some reports propose CM supplementation to be anti-inflammatory, and to reduce exercise-induced oxidative stress (Deminice et al., 2013). In summary, when accepted CM supplementation protocols are followed, the expected increase in intramuscular creatine stores are likely to enhance lean mass, maximal power/strength, and the performance of single and repeated bouts of short-term, high-intensity exercise.

Nitrate

Dietary nitrate (NO_3^-) is a popular supplement initially found to improve oxygen uptake (VO_2) kinetics during prolonged submaximal exercise (Bailey et al., 2009). The ingestion of dietary NO_3^- leads to an enhanced nitric oxide (NO) bioavailability via the NO_3^--nitrite-NO pathway, a reduction catalyzed initially by bacteria in the mouth and the digestive system (Duncan et al., 1995). NO plays an important role in the modulation of skeletal muscle function (Jones, 2014), with proposed mechanisms for improved exercise performance including a reduced ATP cost of muscle force production, an increased efficiency of mitochondrial respiration, increased blood flow to the muscle, and a decrease in blood flow to VO_2 heterogeneities (Bailey et al., 2010).

Of note, a ~5% reduction in O_2 cost of submaximal exercise following nitrate supplementation, coupled with augmented muscle function, has been associated with large (4–25%) improvements in time to exhaustion (Jones, 2014), with smaller enhancements observed (1–3%) in sport-specific, TT performances (McMahon et al., 2016). To date, there is limited support for beneficial effects during exercise >40 min in duration, however, this is possibly due to the lower relative exercise intensity, and the diminished role of nitrite-driven pathways for NO production (Jones, 2014). Recently, nitrate supplementation has been proposed to enhance the function of type II muscle fibers (Bailey et al., 2015), with improved performance (~3–5%) shown during bouts of high-intensity, intermittent, team-sport exercise of 12–40 min in duration (Thompson et al., 2015; Wylie et al., 2016). However, the evidence remains equivocal for any benefit to exercise tasks of shorter duration (<12 min), with some studies showing no effect of acute supplementation on repeated sprint performance (Reynolds et al., 2016), and others showing significant benefits in single- (1.2%) and repeated-sprint (3.9%) tasks following chronic supplementation for 5 days (Thompson et al., 2016). Differences in these findings may possibly relate to the lower dose of nitrate provided in the acute instance; indeed, a dose-response effect of NO_3^- supplement use has been shown previously, with higher NO_3^- doses having a greater impact on 2,000-m rowing performance (Hoon et al., 2014). The athlete's training status may also affect the supplement efficacy, with greater amounts of nitrate likely needed to produce an effect in higher-level athletes (Jones, 2014). However, the benefit of nitrate supplementation for very highly-trained (elite) athletes requires more research, with some (Nyakayiru et al., 2017; Peeling et al., 2015), but not all (Boorsma et al., 2014), studies showing benefits in such cohorts. Finally, chronic NO_3^- supplementation may facilitate training adaptations when taken prior to key sessions, with greater improvements (8.7% vs. 4.7% in placebo control) seen in maximum work rate following 3 weeks of sprint interval training after ingesting 8 mmol (or 500 mg) of NO_3^- 2.5 hr before each training session (Muggeridge et al., 2017).

Leafy green and root vegetables (i.e., spinach, rocket, celery, beetroot, etc.) are the primary source of dietary NO_3^- (Jones, 2014); however, a recent meta-analysis of 76 nitrate trials showed that *beetroot juice* was the supplemental NO_3^- source used in the majority (76%) of exercise interventions (McMahon et al., 2016). Performance benefits may manifest acutely (i.e., within 2–3 hr) following a NO_3^- bolus of 5–9 mmol (310–560 mg) (i.e., Hoon et al., 2014; Peeling et al., 2015), with recent work highlighting that a cumulative influence of repeated NO_3^- intake (>3 days) may also be beneficial (Thompson et al., 2016; Thompson et al., 2015), especially in well-trained athletes (Jones, 2014). Finally, performance benefits may be maintained for at least 15 days, if consumption of the supplement is continued for this duration (Vanhatalo et al., 2010).

Beta-Alanine

Beta-alanine is the rate-limiting precursor to carnosine, an endogenous intracellular (muscle) buffer, and one of the immediate defenses against the accumulation of protons in the contracting musculature during exercise (Lancha Junior et al., 2015). Daily supplementation with 3.2–6.4 g (~65 mg/kg BM) of beta-alanine, for a minimum of 2–4 weeks can increase skeletal muscle carnosine content (~65% above resting levels), improving tolerance for maximal exercise bouts lasting 30 s to 10 min (Saunders et al., 2016). Small yet significant benefits (~2–3%) of beta-alanine supplementation have been shown in both continuous and intermittent exercise tests; however, sport-specific investigations which highlight the practical implications for intermittent sports are distinctly lacking (Hobson et al., 2012; Saunders et al., 2016). Muscle

carnosine content can be further elevated when supplementation regimes are extended to 10–12 weeks (~80% above resting levels), however, the correlation between muscle changes and magnitude of performance benefit remains unestablished (Saunders et al., 2016). Beta-alanine supplementation may not be as effective in well-trained athletes as their lesser-trained counterparts (Bellinger, 2014), partly due to a diminishing role of carnosine toward intramuscular pH regulation in individuals with an already enhanced buffering capacity. However, the small performance changes observed in well-trained athletes to date (0.2–1.3%; Baguet et al., 2010; Chung et al., 2012) may still be meaningful in the context of an applied competition setting.

Beta-alanine dosing strategies typically involve split doses consumed over the day (i.e., 0.8–1.6 g every 3–4 hr), and/or slow release formulations to minimize the likelihood of side effects (Saunders et al., 2016), which may range from itchiness and skin rashes through to episodes of transient paresthesia (Stellingwerff et al., 2012). However, large interindividual variations in muscle carnosine synthesis have been reported following beta-alanine supplementation, postulated to have an inverse association with (a) the individual's preingestion levels of carnosine, (b) the individual's training status, and (c) the proportion of fast-twitch muscle fibers (Nassis et al., 2016). However, in accounting for this individual variation, an in-depth analysis and summary of the available literature by Stellingwerff et al. (2012) proposes that, in order to achieve an approximate 50% increase in muscle carnosine, a total of ~230 g of beta-alanine should be consumed, encompassing a daily consumption range of 1.6–6.4 g/day. Regardless, it is likely that an individualized approach to beta-alanine supplementation should be considered where possible.

In summary, beta-alanine supplementation via the split dose ingestion of ~3.2–6.4 g (~65 mg/kg BM) per day, consumed for a minimum of 2–4 weeks, and up to 12 weeks, should occur in order to augment high-intensity exercise performance ranging from 30 s to 10 min in duration.

Sodium Bicarbonate

Ingestion of sodium bicarbonate ($NaHCO_3$) is proposed to enhance high-intensity exercise performance as an extracellular (blood) buffer; however, the mechanisms of action are complex (Siegler et al., 2016). Although playing an important role in the maintenance of both intracellular and extracellular pH, $NaHCO_3$ is unable to permeate the sarcolemma, and therefore aids intracellular pH regulation indirectly by raising both extracellular pH and HCO_3^- concentrations (Katz et al., 1984; Lancha Junior et al., 2015). This effectively increases the pH gradient between the intracellular and extracellular environments, leading to an enhanced efflux of H^+ and La^- from the exercising muscle during high-intensity activity (Katz et al., 1984; Mainwood & Worsley-Brown, 1975).

While $NaHCO_3$ ingestion is associated with a high level of intraindividual variability in performance outcomes, benefits are generally seen in short-term, high-intensity sprints lasting ~60 s in duration (mean performance enhancement of ~2%), with a diminishing return as the effort duration exceeds ~10 min (Carr, Hopkins, & Gore, 2011); however, greater benefits may be realized (>8% improvement) with a greater number of repeated sprint bouts (Lancha Junior et al., 2015). Successful supplementation protocols typically involve acute $NaHCO_3$ doses of 0.2–0.4 g/kg BM, with time to peak HCO_3^- concentration occurring 60–150 min postingestion (Carr, Hopkins, & Gore, 2011; Siegler et al., 2012). However, common side effects include GI upset, which may negate any performance enhancements, likely explaining the large variability in individual responses (Carr, Slater, et al., 2011). Strategies to minimize GI upset include co-ingesting $NaHCO_3$ with a small, carbohydrate-rich meal (~1.5 g/kg BM carbohydrates) (Carr, Slater, et al., 2011); splitting an acute dose into several smaller doses taken over the course of 30–60 min (Krustrup et al., 2015); or "serially" loading with 3–4 smaller doses per day for 2–4 consecutive days prior to an event (Burke, 2013). Furthermore, sodium citrate has been proposed as an alternative to $NaHCO_3$, as a result of lower reported rates (albeit not in all investigations) of GI upset (Requena et al., 2005).

Summary Point for Established Performance Supplements

It should be considered that each of the supplements listed above may be found in foods considered to be a part of the "everyday diet". Potentially, the aforementioned supplement doses and performance effects are achievable from slightly-elevated dietary consumption of commonly-consumed foods and beverages (i.e., caffeine through coffee intake, and nitrate through leafy green and root vegetable consumption); however, in other cases (i.e., creatine, beta-alanine, and sodium bicarbonate), it may be hard to obtain the required volume without a dedicated supplement source. Regardless, it is no doubt reassuring that each of these established performance supplements can be found in various forms on the shelves and in the fridges of the local supermarket.

Equivocal Performance Supplements

The following supplements are also used by athletes; however, the evidence-base for their potential to enhance athletic performance is less clear.

Sodium Citrate

Similar to $NaHCO_3$, sodium citrate acts as a blood buffer by increasing pH in the extracellular environment, and increasing the gradient between the blood and the active muscle. This is achieved by the dissociation of sodium citrate into its constituent ions, leading to a decrease in $[H^+]$ and an increase in $[HCO_3^-]$ as electrical equilibrium is restored (Requena et al., 2005).

Early studies trialed sodium citrate doses ranging from 0.1 to 0.5 g/kg BM, consumed 90 min prior to a 60-s maximal sprint test. Here, a dose response was seen, with ergogenic benefits requiring a minimum ingestion of 0.3 g/kg BM, which increased proportionally with the amount of supplement consumed (McNaughton, 1990). Subsequently, a 0.5 g/kg BM dose was reported to achieve a ~12% increase in total work completed over exercise tasks lasting 2–4 min (McNaughton & Cedaro, 1992), but higher doses (0.7–0.9 g/kg BM) were found to increase the symptoms of GI distress without increasing the degree of alkalosis produced (Urwin et al., 2016). The more recent discovery that the time to peak blood pH occurs 180–240 min after sodium citrate ingestion suggests that the dosing protocol should occur at a minimum of 3 hr preexercise (Urwin et al., 2016).

Despite these few positive investigations, it should be noted that the ergogenic effect of sodium citrate ingestion remains equivocal, with a previous meta-analysis highlighting a negligible benefit ($0.0 \pm 1.3\%$ improvement) associated with the use of this supplement (Carr, Hopkins, & Gore, 2011). Considering the detrimental side effects from both $NaHCO_3$ and citrate, and the

potential for limited benefits with the latter, athletes and support staff are encouraged to carefully trial the use of these blood buffers in training before implementing an individualized and bespoke protocol in a competition setting.

Phosphates

Numerous hypotheses have been proposed to support the potential benefits of phosphate supplementation on athletic performance (see Buck et al., 2013). The proposed mechanisms underpinning these benefits include an enhanced rate of ATP and PCr resynthesis (Kreider, 1999); improved buffering capacity to support high rates of anaerobic glycolysis (Kreider, 1999); improvement of myocardial contractility leading to increased cardiac efficiency (Kreider et al., 1992); and an increased erythrocyte 2,3 diphosphoglycerate (2,3 DPG) concentration, leading to a reduced affinity of oxygen with hemoglobin and a greater unloading of oxygen to the peripheral tissues (Benesch & Benesch, 1969).

Current investigations of phosphate supplementation (sodium, calcium, or potassium phosphate) have focused on the physiological and performance-related outcomes of laboratory protocols including graded exercise tests to exhaustion, the 30-s Wingate test, 6 × 20 m (~3–4 s) repeat sprint efforts, and TT situations ranging in duration from 3–60 min. Overall, there is equivocal evidence of performance enhancement from phosphate supplementation. In some instances, phosphate has been shown to enhance VO_{2max} (Cade et al., 1984; Kreider et al., 1990), anaerobic threshold (Kreider et al., 1990), and cycling TT performance (Folland et al., 2008). However, in the case of repeated sprints, the magnitude of benefit has been shown to be varied and unclear (Kopec et al, 2016). Finally, there is also a large amount of contrary evidence from the same physiological and performance measures that suggests phosphate supplementation (in isolation, or in combination with other buffer agents) has no impact on exercise capacity or performance outcomes (Brewer et al., 2014; Goss et al., 2001; Kraemer et al., 1995; West et al., 2012). No doubt, the lack of clear consensus defined by this collective work is explained by variations in the supplement protocol used (i.e., differences in dose, type, exercise protocol, etc.) as well as individual responses to the supplement itself (Peeling, 2015).

Typically, phosphate supplementation is achieved over a 3–6 day period, with a total daily dose of ~50 mg/kg of fat-free mass (~3–4 g) consumed in single or split doses throughout the day. This is often associated with GI distress (Cade et al., 1984; West et al., 2012); however, tolerance is improved by concurrent consumption with ~300 ml of a carbohydrate-rich fluid (Brewer et al., 2013). Nevertheless, current evidence regarding the efficacy of phosphate supplementation remains unclear, since there exists no evidence to suggest an accumulation of this supplement in the muscle, where a number of the reported mechanism are suggested to take effect. As such, the use of this supplement for enhanced athletic performance is likely questionable, with further research needed to fully explore its true effect. If considered for use, individual responses should be thoroughly trialed prior to using this supplement in a competition setting.

Carnitine

Carnitine is a compound predominantly found (95%) within the skeletal muscle, playing several important roles in substrate utilization. Carnitine assists in the translocation of long-chain fatty acids into the mitochondria for beta-oxidation, as well as providing a sink for excess production of acetyl-CoA, thus assisting the flux of carbohydrate through the citric acid cycle (see Stephens, Constantin-Teodosiu, & Greenhaff, 2007). Increased muscle carnitine stores via supplementation with L-carnitine are postulated to spare glycogen, via increased fat oxidation, at lower exercise intensities, and to promote more efficient carbohydrate oxidation and reduced lactate accumulation at higher intensities, delaying the onset of fatigue during endurance-based activity.

Research on L-carnitine supplementation has shown equivocal outcomes. Marconi et al. (1985) reported a 6% increase in VO_{2max} during graded treadmill running, but no change in steady-state VO_2 or fuel utilization during submaximal (65% VO_{2max}) exercise when 1 g of L-carnitine was consumed every 6 hr for 2 weeks. Additionally, Greig and colleagues (1987) found no effects on either VO_{2max} or substrate metabolism with L-carnitine supplementation provided as 2 g/day in split doses for 2–4 weeks. Of note, the lack of performance effect seen in these studies may likely result from the fact that muscle carnitine levels do not seem to increase when using these standard supplement protocols (i.e., up to 4 g/day for 14 days; Barnett et al., 1994). More recently, Novakova et al. (2016) suggested that 12 weeks of L-carnitine supplementation (2 g/day in split doses) was associated with a ~20% increase in the plasma carnitine levels of habitual meat eaters, and a ~30% increase in vegetarians. However, this failed to change muscle carnitine levels in the meat-eating group, and only translated to a 13% increase in the vegetarians (who had started the trial with ~10% lower muscle carnitine levels). Importantly, there was no effect on muscle function, energy metabolism, or VO_2 during either submaximal or maximal exercise tests.

It is likely that the lack of efficacy of oral L-carnitine supplementation in many studies is due to its low bioavailability and failure to increase muscle carnitine stores. However, Stephens, Evans, et al. (2007) have shown that whole body carnitine retention can be increased when the supplement is co-ingested with a substantial carbohydrate source to take advantage of an insulin-mediated uptake (i.e., 3 g/day consumed with 94 g CHO), over long periods (i.e., 100 days to increase muscle carnitine by ~10%). In a follow-up study (Wall et al., 2011), chronic supplementation (twice daily intake of 2 g L-carnitine plus 80 g of carbohydrate, for 24 weeks) increased muscle carnitine by 21%, resulting in a 55% reduction in muscle glycogen utilization during submaximal cycling (30 min @ 50% VO_{2max}), better matching of metabolic flux during high-intensity cycling (30 min @ 80% VO_{2max}), and an increased work output (+11%) during a 30-min "open-intensity" performance trial (attributed to a reduced anaerobic ATP production). Regardless of these performance benefits, it is likely that these aforementioned ingestion protocols are impractical on a daily basis, and it is also unclear as to the impact that such a dosage regime may have on the individual's health. Therefore, given the limited research in this space, and the considerable effort needed to implement such a protocol, further investigation is needed to clarify the efficacy and safety of following these prolonged supplement regimes.

Developing Performance Supplements

This section covers supplements which are emerging in both their popularity and the evidence base for athletic performance benefits. However, more work is needed before conclusive recommendations can be made on their use, and there may be some differences in the principles or mechanisms by which they could be of value. The performance supplements outlined in the prior sections are

presented in view of a strong evidence base to reflect a *direct impact* on athletic performance through the augmentation of various rate-limiting processes. However, other supplements may have an *indirect impact* on performance via their ability to support the training process, through their influence on factors such as inflammatory modulation, oxidative stress, and signaling pathways for adaptation, or their ability to support repetitive performance by restoring homeostasis between two exercise bouts. For example, the amino acid N-acetylcysteine acts as an anti-oxidant that may assist in athlete recovery through mediation with exercise-induced reactive oxygen species (see Braakhuis & Hopkins, 2015). Such an outcome may impact athlete performance—for instance, if the supplement protocol targets an improvement in fatigue resistance during heavy competition schedules. Similarly, food polyphenols may act in a comparable way, possessing strong anti-oxidant and anti-inflammatory properties (see Tsao, 2010) that may be beneficial to exercise recovery. For instance, the high anthocyanin content of tart Montmorency cherries has been shown to reduce the inflammatory and oxidative stress responses to marathon running (Howatson et al., 2010) and during consecutive days of stochastic, high-intensity cycling (Bell et al., 2014). Of note, only blood biomarkers were presented in these aforementioned studies to suggest such a benefit and, therefore, these outcomes should be further confirmed by muscle analysis in future research.

Of note, there are several issues that make it more difficult to substantiate the performance benefits of these supplements. One factor is that it may take a lengthy period before better recovery between exercise bouts or better support of training leads to a detectable improvement in competition performance. Second, there is the possibility that better preservation/restoration of homeostasis, or dampening of the inflammatory and oxidative stress incurred during training sessions, might *reduce* the adaptation to the exercise stimulus. For example, previous research on supplementation with anti-oxidant vitamins (i.e., vitamins C and E) has shown a reduction in the cellular signaling pathways which underpin the adaptive response to exercise, decreasing the overall training response and reducing any potential improvements to performance (Gomez-Cabrera et al., 2008). As such, the ultimate benefit of the use of these supplements may depend on how and when they are used; for example, they might be used in scenarios of repeated competition events to reduce exercise perturbations and enhance recovery and subsequent performance, but avoided during training bouts where optimal adaptation is driven by full exposure to oxidative or inflammatory stress.

Alternatively, some supplements may affect a number of body systems, with positive effects on one system counteracting the minor negative effects on another. For example, although they are considered to have anti-oxidant properties, some polyphenol subclasses (e.g., the flavonoids) are postulated to enhance the exercise-induced signaling pathways that stimulate mitochondrial biogenesis and changes in vascular function (see Somerville et al., 2017). Furthermore, numerous food polyphenols are also suggested to have a *direct effect* on performance, potentially a result of mechanisms relevant to flow mediated dilatation, NO production, and adenosine receptor antagonism effects (Somerville et al., 2017). For instance, a daily dose of New Zealand blackcurrant extract (300 mg containing 105 mg of anthocyanins) for a period of 7 days has been suggested to enhance endurance performance by 2–3% during running (5 km) and cycling-based (16.1 km) TT activities (Cook et al., 2015; Perkins et al., 2015); and a 500–1,000 mg daily dose of quercetin (consumed over extended periods ranging from 1–8 weeks) has shown clear moderate improvements (+2.8%) to performance when mediating the type of athletic event undertaken (Somerville et al., 2017). However, clearly in its infancy, there exists a need for further research exploring these emerging supplements to fully examine the effects and potential efficacy of their ability to support the training process, and to provide a direct positive impact on athletic performance.

Concluding Remarks

This review summarizes the evidence for a number of commonly-used supplements, ingested with the aim of enhancing athletic performance. The focus here was on products which have a clear mechanism/function that may be relevant to a given type of sporting activity, as well as a body of research that has investigated the translation of this mechanism into a detectable performance improvement. This type of information allows the coach, athlete, and/or support team to make informed choices about performance supplements that may be relevant to their situation. This should be further viewed in light of the marginal, but often important, gains that may be achieved through sound use of these products, as well as practical considerations such as a lack of uniform tolerance and response to a given supplement. As such, any use of performance supplements should be thoroughly trialed in training before implementation into a competition environment, since, in some scenarios, outcomes ranging from a lack of efficacy to deleterious responses may outweigh any expected performance enhancement.

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