Legal pre-event nutritional supplements to assist energy metabolism

Lawrence L. Spriet¹, Christopher G.R. Perry and Jason L. Talanian

Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada N1G 2W1

Abstract

Physical training and proper nutrition are paramount for success in sport. A key tissue is skeletal muscle, as the metabolic pathways that produce energy or ATP allow the muscles to complete the many activities critical to success in sport. The energy-producing pathways must rapidly respond to the need for ATP during sport and produce energy at a faster rate or for a longer duration through training and proper nutrition which should translate into improved performance in sport activities. There is also continual interest in the possibility that nutritional supplements could further improve muscle metabolism and the provision of energy during sport. Most legal sports supplements do not improve performance following oral ingestion. However, three legal supplements that have received significant attention over the years include creatine, carnitine and sodium bicarbonate. The ingestion of large amounts of creatine for 4–6 days increases skeletal muscle creatine and phosphocreatine contents. The majority of the experimental evidence suggests that creatine supplementation can improve short-term exercise performance, especially in sports that require repeated short-term sprints. It may also augment the accretion of skeletal muscle when taken in combination with a

¹To whom correspondence should be addressed (email lspriet@uoguelph.ca).
resistance-exercise training programme. Supplementary carnitine has been touted to increase the uptake and oxidation of fat in the mitochondria. However, muscle carnitine levels are not augmented following oral carnitine supplementation and the majority of well-controlled studies have reported no effect of carnitine on enhancing fat oxidation, $V_{O_2\text{max}}$ or prolonged endurance exercise performance. The ingestion of sodium bicarbonate before intense exercise decreases the blood [H+] to potentially assist the efflux of H+ from the muscle and temper the metabolic acidosis associated with intense exercise. Many studies have reported performance increases in laboratory-based cycling tests and simulated running races in the field following sodium bicarbonate ingestion where the need for ATP from substrate phosphorylation is high. However, other studies have reported no benefit and the incidence of negative side effects is high.

Introduction

The ability of skeletal muscle to rapidly convert chemical into mechanical energy for physical activity makes it a most remarkable organ. The need for ATP in muscles can increase more than 100-fold when moving from rest to strenuous exercise. The metabolic pathways that produce ATP do a remarkable job as the [ATP] is well-maintained in most exercise and sport situations and only decreases by 25–40% during maximal sprinting. The ATP for most exercise and sporting activities is produced in the mitochondria via oxidative phosphorylation. The inputs for mitochondrial ATP production are oxygen, ADP, inorganic phosphate and the donation of electrons from the metabolism of the foods we eat (mainly carbohydrate and fat). Skeletal muscle can also produce ATP without oxygen via substrate phosphorylation with the main sources being the glycolytic pathway with the formation of lactate and the degradation of phosphocreatine.

Athletes and coaches want to know how we can maximize the ability of our muscles to provide energy during training and sporting events. The main avenues for improving energy provision during exercise are proper training and sound nutritional regimens which increase the supply of intramuscular fuels (glycogen, triacylglycerol) and the availability and uptake of blood-borne fuels (glucose, non-esterified fatty acids). The muscle also adapts to exercise training by producing more mitochondria and blood vessels and by generally speeding up all metabolic processes. The premise is that producing energy at a faster rate and for a longer duration should translate into improved performance in sport activities. Once training adaptations and nutritional regimens have been optimized, athletes and coaches also want to know whether sports supplements further improve muscle metabolism. In addition, if nutrition and training are not optimal, owing to injury for example, could supplementation substitute for the lack of training and improve muscle metabolism? Most nutritional sports supplements given orally do not work and it is generally unrealistic to expect that a supplement will improve muscle metabolism because most metabolic processes
are tightly regulated. In most cases, attempts to augment the content of a fuel, transport protein, ion, amino acid, by-product or pathway metabolite through supplementation have already been optimized by the muscle cell in response to the repeated demands of exercise.

This chapter will examine three compounds (creatine, carnitine and sodium bicarbonate) that are considered legal sports supplements, they have received significant research attention and have been suggested to assist muscle metabolism and energy supply and ultimately improve sport performance.

Creatine supplementation

α-Methylguanidine acetic acid or creatine is found primarily in skeletal muscle and can form the high-energy phosphate compound phosphocreatine. The daily creatine requirement is approx. 2 g/day [1]. Dietary intake of creatine from meat and fish is approx. 1 g/day, whereas endogenous creatine production in the liver, pancreas and kidneys accounts for the remaining daily creatine requirement. Creatine is delivered to skeletal muscle in the blood and enters the muscle against a concentration gradient via a creatine transporter.

Role of creatine in energy metabolism

The phosphocreatine content in muscle is about 3–3.5 times that of ATP, the immediate source of energy in muscle cells [2]. Phosphocreatine can rephosphorylate ADP to ATP via the near-equilibrium creatine kinase reaction through the transfer of a phosphate group. Phosphocreatine and the production of ATP in the glycolytic pathway with lactate formation provide two important substrate phosphorylation mechanisms to provide energy in skeletal muscle when aerobic or oxidative phosphorylation cannot meet the demand for ATP. This occurs most commonly during the transition from rest to exercise or from one power output to a higher power output where substrate phosphorylation or ‘anaerobic’ energy production provides ATP while the slower responding aerobic ATP production pathways are completely activated. Anaerobic energy provision is also very important during high-intensity exercise when the power output is above 100% of the maximal oxygen uptake ($V_{O2\text{max}}$). In this situation, aerobic metabolism is not able to match the ATP demand and a large contribution of energy is supplied from phosphocreatine and the glycolytic pathway. Although these two anaerobic sources of energy are very quick to respond and can provide ATP at high rates during exercise, their capacities are limited and can only be sustained for a short period of time. Total creatine content in human skeletal muscle averages approx. 125 mmol/kg of dry muscle with 60–70% of the creatine bound to phosphate (phosphocreatine, approx. 75–90 mmol/kg of dry muscle). There is a large inter-individual variation in total muscle creatine content ranging from approx. 100–150 mmol/kg of dry muscle. Total muscle [creatine] is maintained by moving creatine into the muscle against a concentration gradient via a Na+- and Cl-–dependent transporter [3,4]. Interestingly, muscle total creatine and phosphocreatine
levels do not increase following aerobic, sprint or resistance-training, unlike the training-induced improvements that occur with aerobic energy production and ATP provision from anaerobic glycolysis. Commercially available creatine supplementation has become a popular ergogenic aid and is believed to improve sprint performance [5] and increase the rate of muscle mass gain when engaged in resistance-training [6].

**Pioneering work with creatine supplementation**

Only 15 years ago, Harris et al. [7] began an in-depth examination of the effects of oral creatine supplementation on muscle creatine levels. They were aware of the fact that creatine-deficient patients increased their muscle strength and exercise performance following oral creatine supplementation and concluded that this effect must be muscle based. Their work revealed that a single 5 g creatine dose increased the plasma [creatine] from approx. 50 μM to as high as 600–1000 μM and the concentration was still elevated at approx. 200–400 μM after 4–5 h. Harris et al. [7] also demonstrated that 5 g doses of creatine, 4–6 times a day maintained very high plasma [creatine] throughout the day and led to increased total muscle creatine content in normal healthy subjects. Using this dosing regimen, 15 out of 17 participants (5 females, 12 males) increased their total muscle creatine content by approx. 20 mmol/kg of dry muscle and phosphocreatine content by approx. 8 mmol/kg of dry muscle with 4–7 days of creatine supplementation, with no observed increase in ATP concentration. Supplementation beyond 4–7 days did not produce any further increases in total creatine. The two non-responders to creatine supplementation already had a high total muscle creatine content (approx. 145 mmol/kg of dry muscle) prior to supplementation, which was similar to the total creatine content in all of the responding subjects following supplementation. These results have been corroborated in many laboratories around the world in the intervening years [8] and it has also been shown that creatine supplementation produces large increases in both fibre types I and II in human skeletal muscle [9].

Hultman et al. [10] also reported that ingestion of a so-called ‘maintenance dose’ of 2 g of creatine/day following the rapid-loading phase maintained the higher creatine content for 35 days. However, van Loon et al. [11] found that ingestion of a maintenance dose of 2 g of creatine/day following the rapid loading phase was not sufficient to keep total creatine content elevated to the extent observed following rapid loading. A maintenance dose of 3–5 g/day may be in order to ensure the new higher [creatine] is maintained. Hultman et al. [10] and others have also demonstrated that the muscle [creatine] returns to normal levels 5–7 weeks after the cessation of rapid creatine loading when no maintenance dose is given (4–7 days of approx. 20 g of creatine/day).

Additional work demonstrated that ingesting approx. 93 g of carbohydrate with each of the four daily 5 g creatine doses during the rapid loading phase increased muscle creatine by an additional 10–12 mmol/kg of dry muscle as compared with a group without carbohydrate [12]. This work was substantiated...
by others that showed creatine supplementation (5 g/day) with carbohydrate (approx. 100 g/day) increased total creatine by approx. 37 mmol/kg of dry muscle following 6 days of supplementation [11]. The augmented muscle creatine content with carbohydrate ingestion appears to be the result of the increase in circulating insulin stimulating the creatine transporters [12].

**Potential effects of increased muscle creatine content on exercise performance**

Once it was established that creatine supplementation could increase skeletal muscle total creatine and phosphocreatine contents, attention turned to the potential effects these changes may have on cellular function during exercise (Figure 1). Three main areas of potential interest are (1) the possibility that exercise requiring high rates of ATP provision may be enhanced due to a higher muscle [phosphocreatine]; (2) creatine-induced increases in cell osmolarity leading to cell swelling and the stimulation of anabolic processes, which, when combined with the additional anabolic stimulus of resistance training, may lead to a greater accretion of muscle mass; and (3) involvement of phosphocreatine and creatine in the so-called ‘phosphocreatine shuttle’ and the possibility that ATP produced in the mitochondria may be moved to the sites of ATP utilization more efficiently during intense exercise [8].

**Effects of creatine supplementation on short-term high-intensity performance**

Greenhaff et al. [13] first revealed that increasing muscle [phosphocreatine] content through creatine supplementation increased repeated muscle torque...
production during intense exercise compared with a group supplemented with a placebo. Reviews assessing the effects of creatine supplementation on short-term sprints, resistance and maximal-intensity type exercises have predominantly demonstrated improved performance in a laboratory setting, with no studies observing a negative effect of creatine supplementation on performance [8]. The majority of evidence suggests that the greatest improvements in performance following creatine supplementation are in repetitive high-intensity exercise bouts [1], which would benefit athletes in sports where repeated short-term sprints and ballistic movements are required.

**Effects of creatine supplementation on skeletal muscle hypertrophy during resistance training**

Evidence also suggests that creatine supplementation can augment the muscle hypertrophy that accompanies resistance training. Volek et al. [14] reported that 12 weeks of creatine supplementation coupled with resistance exercise resulted in greater type I and II muscle fibre cross-sectional area compared with those training on a placebo. Also, young female volunteers that resistance-trained for 10 weeks with creatine supplementation showed greater improvements in maximal intermittent exercise capacity and fat-free mass than those training on a placebo [6]. Although others have corroborated these results, Tarnopolsky et al. [15] reported that the increases in muscle hypertrophy observed following 8 weeks of resistance training while supplementing with creatine plus glucose were similar to increases in hypertrophy following supplementation with glucose plus protein. Recently, it has been shown that the timing of creatine intake can also influence the adaptations to creatine supplementation [16]. Following 10 weeks of resistance training and creatine supplementation, participants taking creatine supplements (approx. 11 g/day) prior to and immediately following exercise showed greater increases in lean body mass and strength compared with participants taking creatine supplements in the morning and evening.

The larger increases in lean body mass following creatine supplementation have been suggested to result from augmented water retention in the muscle such that an increase in cell osmolarity may further stimulate the proteins that activate net anabolic processes. These may include increased protein synthesis, a reduction in protein catabolism and/or a shift in the phosphocreatine/creatine ratio altering cell signalling [17,18].

**Effects of creatine supplementation on aerobic function**

The literature examining the potential for creatine supplementation to augment aerobic exercise in a positive way has reported no beneficial effect on $V_{\text{O}_2\text{max}}$, submaximal $V_{\text{O}_2}$, or endurance capacity [8].

**Conclusions**

In summary, oral supplementation of 5 g of creatine/day for 4–7 days increases total muscle creatine content by approx. 15–20% and muscle phosphocreatine by approx. 10%. The majority of the experimental evidence suggests that
creatine supplementation can improve short-term intense exercise performance and is best suited to improve exercises/sports that require repeated short-term intense efforts. The literature also suggests that creatine supplementation may augment the accretion of skeletal muscle when taken in combination with a resistance-exercise training programme.

Carnitine supplementation

L-Carnitine (1-3-hydroxy-4-trimethylaminobutyric acid) exists primarily in skeletal muscle (approx. 95% of approx. 20 g in the body). The normal diet appears to provide enough carnitine or, alternatively, provides enough of the amino acids lysine and methionine to synthesize the required carnitine in the liver and kidney on a daily basis. Carnitine is delivered to skeletal muscle in the blood and gains entry into the muscle against a concentration gradient via a specific transporter [19].

Role of carnitine in energy metabolism

Carnitine plays two essential roles in skeletal muscle energy metabolism. Carnitine is involved in the transport of LCFAs (long-chain fatty acids) from the cytoplasm across the mitochondrial membranes for subsequent entry into the β-oxidation pathway in the mitochondrial matrix [20] (Figure 2). LCFA transport is linked to the CPT (carnitine palmitoyltransferase) complex and the FAT/CD36 (fatty acid transport protein). CPT I exists in

Figure 2. Schematic representation of the involvement of creatine in the transport of LCFAs across the mitochondrial membranes and in the buffering of excess acetyl-CoA production in skeletal muscle

CACT, carnitine-acylcarnitine translocase; G6P, glucose 6-phosphate; IMS, inner mitochondrial space; OMM and IMM, outer and inner mitochondrial membranes.
the outer mitochondrial membrane and catalyses the transfer of cytoplasmic LCFA-CoA to acylcarnitine. The acylcarnitine is then transported across the outer membrane, the inter-membrane space and the inner mitochondrial membrane in some presently unknown manner by FAT/CD36 and carnitine-acylcarnitine translocase. CPT II reconverts the acylcarnitine into LCFA-CoA in the mitochondrial matrix. The transfer of LCFAs into the mitochondria does not consume carnitine as it is moved back to the cytoplasm, presumably by carnitine-acylcarnitine translocase. An increase in LCFA-CoA in the mitochondrial matrix facilitates an increase in β-oxidation, with the production of reducing equivalents for the electron transport chain and acetyl-CoA for the TCA (tricarboxylic acid) cycle.

Carnitine also plays a role in buffering the rise in acetyl-CoA that occurs at the onset of moderate and intense exercise. Several studies have shown glycolysis-induced increases in muscle acetyl-CoA and acylcarnitine at the onset of exercise at various power outputs [21,22]. This suggests that the production of acetyl-CoA is in excess of the TCA cycle needs and the extra acetyl-CoA is buffered by the action of the near-equilibrium enzyme CAT (carnitine acetyltransferase), which converts acetyl-CoA and carnitine into acetylcarnitine and free CoA (Figure 2). The total CoA content in the mitochondria is finite and unbuffered increases in acetyl-CoA would sequester most of the available free CoA. However, free CoA is a substrate for many important mitochondrial reactions associated with energy production during muscle contractions, including CPT II, PDH (pyruvate dehydrogenase), the dehydrogenases in the TCA cycle and thiolase in the β-oxidation pathway (Figure 2). Although the free [CoA] decreases during exercise, a certain level must be maintained for use as a substrate in these important reactions. In order to maintain the buffering potential of the CAT reaction, much of the formed acetylcarnitine is believed to be transported out of the mitochondria. A small portion of the cytoplasmic acetylcarnitine may be reconverted into acetyl-CoA and carnitine, but most appears to remain as acetylcarnitine. During prolonged moderate intensity exercise when muscle acetyl-CoA production decreases, some of the acetylcarnitine may be returned to the mitochondria and provide acetyl-CoA for the TCA cycle. However, in most exercise situations the acetylcarnitine returns to the mitochondria and ultimately acetyl-CoA following exercise.

**Could the muscle carnitine content limit fat oxidation during intense aerobic exercise?**

There are pools of free carnitine in the cytoplasm and mitochondria. It has been repeatedly demonstrated that the free carnitine content decreases and acylcarnitine increases in human skeletal muscle with increasing exercise intensity [21–23]. It is not clear, however, what happens to the mitochondrial and cytoplasmic pools of these compounds during exercise and whether the availability of carnitine ever limits LCFA transport or acetyl-CoA buffering. At a moderate exercise intensity of approx. 60–65% \( \dot{V}O_2_{max} \) the free carnitine content decreases to buffer some of the increase in acetyl-CoA. However, this
occurs at a time when LCFA transport reaches its maximum level, leading to the conclusion that the free [carnitine] does not limit LCFA transport at this intensity. Although free CoA also decreases at approx. 60–65% $V_o_{2max}$, fat oxidation is at its peak, leading to the conclusion that there is sufficient free CoA to sustain the key metabolic reactions in the mitochondria. Free carnitine and CoA are not consumed in these processes, simply cycled. However, when moving to intense exercise (approx. 90% $V_o_{2max}$), acetyl-CoA and acetylcarnitine content increases further and free CoA and carnitine content decreases to a greater extent than at 65% $V_o_{2max}$. So while the production of oxidative energy is at its highest level in the mitochondria, the free CoA content is at its lowest! This leads to the conclusion that there is still sufficient free CoA and that it does not limit the key reactions providing reducing equivalents for the electron transport chain. However, could the further decrease in free carnitine become limiting for the transport of LCFA into the mitochondria and help explain the decrease in fat oxidation that occurs at this higher intensity? It has been hypothesized that free carnitine may become limiting to LCFA transport via the CPT–FAT/CD36 complex if the content falls below 6 mmol/kg of dry muscle, as can happen during intense exercise (resting levels are approx. 20 mmol/kg of dry muscle) [22], but testing this suggestion has been difficult. The major problem has been the inability to successfully manipulate the muscle or more specifically the cytoplasmic [carnitine] during exercise.

**Oral carnitine supplementation does not increase skeletal muscle carnitine content**

The important roles of carnitine in energy metabolism have spurred many investigators to examine the effects of oral carnitine supplementation on the ability of skeletal muscle to increase reliance on fat as the principle substrate for energy production during exercise and potentially improve exercise performance. The underlying assumption of these studies is that carnitine limits fat transport into the mitochondria and that the provision of additional carnitine in the diet and appearance in the plasma would result in an increased muscle carnitine content, increased LCFA transport into the mitochondria and increased fat oxidation. An increased reliance on fat during intense exercise could reduce the need for carbohydrate at a given exercise power output, delay the depletion of muscle carbohydrate stores and potentially prolong time to exhaustion. Another possibility is that a higher maximal rate of fat oxidation may allow for a higher $V_o_{2max}$, a higher exercise power output and reduced time to complete a set task. However, this seems unlikely as most evidence suggests that oxygen delivery to the working muscles and not fuel availability limits $V_o_{2max}$ [24]. As reviewed several times, numerous studies have demonstrated that oral carnitine supplementation for 2 weeks to 3 months does not increase skeletal muscle carnitine content, and therefore cannot alter muscle metabolism during exercise [8,25–27]. In keeping with this finding, the majority of well-controlled studies on this topic have reported no effect of carnitine
supplementation on enhancing fat oxidation, reducing carbohydrate oxidation, glycogen breakdown or lactate accumulation, enhancing performance during prolonged endurance exercise, or increasing \( \dot{V}O_{2\text{max}} \).

**Why is supplemental carnitine not taken up by skeletal muscle?**

The ingestion of supplementary carnitine produces only modest increases in plasma carnitine concentrations (30–70%) above the resting level of 40–50 μM. The increase is limited by the fact that carnitine passes into the urine when plasma concentrations increase to 60–100 μM [28]. Furthermore, carnitine is taken up into muscle against a large concentration gradient via a carnitine transporter protein [19]. The \( K_m \) of carnitine for the transporter is 4.3 μM, indicating that normally low arterial carnitine concentrations of 40–50 μM would not limit cellular uptake [19]. In addition, once carnitine is in the cytoplasm of the cell, the \( K_m \) of carnitine for CPT-1 is approx. 0.5 mM [20], suggesting that flux through the mitochondrial transport process would not be hindered during any exercise challenge in a healthy individual. This fact undermines the premise that increasing plasma carnitine concentrations will result in increased muscle carnitine content.

It must also be remembered that most muscle measurements of carnitine content target only total muscle concentrations and not compartment levels. It has been reported that type I fibres show a greater decrease in free carnitine than type II fibres during exhaustive exercise despite similar concentrations at rest [29] but there are no reported attempts to measure cytoplasmic and mitochondrial concentrations at varying power outputs during exercise.

**Recent attempts to increase skeletal muscle carnitine content**

Recent work from Greenhaff’s laboratory [30,31] have reported some success in elevating muscle carnitine content by maintaining a high plasma carnitine concentration during a hyperinsulinaemic state. The idea of combining high plasma carnitine concentrations with elevated blood insulin stems from the observations that (i) insulin stimulates \( Na^+/K^+ \) pump ATP-ase activity on the sarcolemma, (ii) carnitine transport into skeletal muscle is \( Na^+ \)-dependent, and (iii) insulin enhances \( Na^+ \)-coupled uptake of other compounds such as creatine and amino acids. Stephens et al. [30,31] reported that a continual 5 h intravenous infusion of carnitine (supraphysiological plasma concentration of approx. 550–600 μM) coupled with an insulin infusion (approx. 150–160 m-units/l) in healthy human subjects resulted in a temporary approx. 15% increase in total muscle carnitine, an approx. 17% increase in free carnitine content and a 2.3-fold increase in carnitine transporter protein mRNA content. The carnitine contents returned to pre-infusion levels 24 h later and no effects were observed when carnitine was infused during a normal insulin state [30].

This protocol also decreased PDH activity and lactate accumulation by the end of the 5 h infusion and increased muscle glycogen content 24 h after the initiation of the carnitine infusion [30]. Collectively, these results hint at a potential enhancement in fat oxidation following approx. 5 h of simultaneous
hypercarnitinaemia and hyperinsulinaemia, but confirmation of this possibility would require more direct measurements. As cited in a recent review [32], it was later demonstrated that a minimum plasma insulin concentration of 90 m-units/l for 5 h also increases plasma carnitine content and that this insulin level can be reached with the ingestion of approx. 100 g of carbohydrate [32]. Nevertheless, although this approach is not practical for use in the sporting world it should assist in answering some basic research questions regarding the importance of carnitine for energy metabolism during intense exercise [32].

Conclusions
Carnitine is essential for the transport of LCFAs into the mitochondria and for buffering the exercise-induced increases in mitochondrial acetyl-CoA during exercise. It is clear that attempts to increase muscle carnitine content by oral carnitine supplementation have been ineffective in healthy individuals. Not surprisingly, the majority of well-controlled studies on this topic have reported no effect of carnitine supplementation on (i) enhancing fat oxidation, (ii) reducing carbohydrate oxidation, glycogen breakdown or lactate accumulation, (iii) enhancing performance during prolonged endurance exercise, and (iv) increasing \( \dot{V}O_{2\text{max}} \). Much remains to be learned regarding the importance of carnitine in regulating fat transport into the mitochondria in contracting skeletal muscle. For example, recent studies where muscle carnitine contents have been temporarily elevated by 10–20% with infusion-induced plasma hypercarnitinaemia and hyperinsulinaemia may be useful in determining whether muscle carnitine levels limits oxidative metabolism during strenuous exercise [30–32].

Sodium bicarbonate loading
During intense exercise at power outputs higher than can be sustained by aerobic energy production alone, phosphocreatine and anaerobic glycolysis provide ATP at high rates. This type of exercise leads to fatigue in several seconds to a few minutes, as the phosphocreatine store is depleted and the ionic changes associated with the high glycolytic rates leads to an accumulation of \( H^+ \) and a state of metabolic acidosis in skeletal muscle. The major contributors to the increased skeletal muscle \( [H^+] \) during intense exercise appear to include the accumulation of lactate (\( La^- \)) ions inside the muscle and the loss of potassium (\( K^+ \)) ions from the muscle [33]. Although skeletal muscle has several cellular-based buffering mechanisms, some of the acid load is moved into the interstitial and blood spaces. A primary buffer in the blood is bicarbonate (\( HCO_3^- \)). It combines with \( H^+ \) to form \( H_2CO_3 \) and immediately dissociates to \( CO_2 \) and \( H_2O \). Much of the produced \( CO_2 \) can be eliminated by the lungs, but this buffer system is not able to prevent increases in muscle and blood \( [H^+] \) during intense exercise. It is also clear that extracellular ion changes (i.e. increased \( [Na^+] \)) can affect ion balances across the muscle membrane and affect membrane depolarization during exercise [34]. Although it remains
controversial, it has long been recognized that changes in many intracellular ions, including $K^+$ and $H^+$, can interfere with skeletal muscle performance at a number of sites in contracting muscle: action potential propagation, excitation–contraction coupling, calcium handling, actin–myosin interaction and the energy-producing pathways [34–36].

Exercise training can increase the muscle buffering capacity but ultimately the magnitude of this adaptation is limited. Not surprisingly, there have been many attempts to artificially increase the buffering capacity of the blood with sodium bicarbonate ($\text{NaHCO}_3$) or sodium citrate ingestion in the hopes of increasing the muscle buffering capacity and/or the rate of $H^+$ efflux from active skeletal muscle during exercise, delaying fatigue and improving exercise performance.

Physicochemical changes associated with sodium bicarbonate and sodium citrate loading
The normal method of inducing metabolic alkalosis in the blood is to ingest gelatin capsules of $\text{NaHCO}_3$ with large amounts of water over a 2–3 h period preceding strenuous exercise. It is normally assumed that the ingested $\text{HCO}_3^-$ is simply absorbed into the blood leading to increases in $[\text{HCO}_3^-]$ and decreases in $[\text{H}^+]$. However, several systems and physicochemical laws govern the $[\text{HCO}_3^-]$ and $[\text{H}^+]$ in aqueous solutions such as the plasma and the interstitial and cytosolic compartments in skeletal muscle [36]. One physicochemical law states that a given solution of body fluid (i.e. plasma) aims to maintain electrical neutrality and releases either $H^+$ or $OH^-$ as appropriate to achieve this goal. This approach suggests that the increase in plasma $[\text{HCO}_3^-]$ that occurs following $\text{NaHCO}_3$ ingestion cannot be simply due to $\text{HCO}_3^-$ absorption alone. As the ingested sodium is absorbed mainly in the small intestine, the gut is left relatively acidic. This leads to an increase in the partial pressure of $\text{CO}_2$ in the gut and a diffusion of $\text{CO}_2$ into plasma. The net effect is then a conversion of $\text{CO}_2$ into $\text{HCO}_3^-$ in the plasma and a fall in $[\text{H}^+]$. In addition, the $Na^+$ absorbed into the plasma is removed in the kidney to precisely regulate the plasma $Na^+$ with the concomitant loss of plasma chloride ($\text{Cl}^-$). The lost $\text{Cl}^-$ is replaced by $\text{HCO}_3^-$ to maintain electrical neutrality and this appears to account for the majority of the fall in $[\text{H}^+]$. This suggestion is supported by the fact that sodium citrate ingestion produces similar increases in plasma $[\text{HCO}_3^-]$ and decreases in $[\text{H}^+]$, as reported following $\text{NaHCO}_3$ ingestion [37].

Effects of sodium bicarbonate loading on exercise performance
The work in this area began approx. 75 years ago when reports by Dennig et al. and Margaria et al. (reviewed in [36]) both reported that 10–20 g of $\text{NaHCO}_3$ prolonged treadmill running to exhaustion lasting 4–7 min in a single subject in each study. Little work appeared until the mid 1970s when two studies reported giving subjects approx. 0.3 g of $\text{NaHCO}_3$/kg of body mass (21 g
Several studies followed from 1980–2000, but the effect of NaHCO₃ ingestion on improving performance was not overly convincing [36,38]. There were almost as many studies reporting no effect of NaHCO₃ ingestion as there were reporting positive effects. There appeared to be a trend for NaHCO₃ ingestion to improve performance in events lasting from approx. 1–5 min but not in events lasting less than 50 s, or longer than 5–10 min. A good example of these conflicting findings can be seen in the published reports that examined running performance during simulated races of 400, 800 and 1500 m. Goldfinch et al. [39] reported that NaHCO₃ improved 400 m run time from 58.5 to 56.9 s, while Kindermann et al. [40] reported no effect. Wilkes et al. [41] reported that 800 m run time improved from 2:05.9 min in control conditions and 2:05.1 min following placebo ingestion to 2:02.9 min following NaHCO₃ ingestion. However, McKenzie et al. [42] reported no effect of NaHCO₃ on 800 m run time. Lastly, Bird et al. [43] also reported that NaHCO₃ improved 1500 m run time (approx. 4:15 min) by approx. 3–4 s. Many of the variables that would be expected to account for this inconsistency in performance effects were controlled. None of the runners in the studies were elite, but all were well-trained, actively competing and members of track teams. All studies gave subjects between 0.3–0.4 g of NaHCO₃/kg of body mass approx. 90–180 min before competing in the simulated running races. However, many of the studies had low numbers of subjects, which makes statistical significance difficult to achieve. Also, a common problem with the administration of NaHCO₃ is gastrointestinal stress leading to vomiting and diarrhoea. Some subjects also report dizziness or a feeling of general malaise. Although these side effects are not serious in terms of health, they can be very debilitating during competitions and easily limit any potential benefits of NaHCO₃ ingestion.

Publications since 2000 appear to more clearly point to performance increases following NaHCO₃ ingestion [34,38,44–46], although these studies did not employ races in the field and were laboratory-based performance tests.

**Effects of sodium bicarbonate ingestion on skeletal muscle acid-base status**

The studies that have measured plasma [HCO₃⁻] and [H⁺] following the ingestion of 0.2–0.4 g of NaHCO₃/kg of body mass are consistent in reporting that [HCO₃⁻] is increased and [H⁺] is reduced [33,41]. However, it appears that these changes are generally not sufficient to decrease skeletal muscle [H⁺] at rest [44]. Muscle La⁻ content and buffering capacity are also not affected. This implies that any improvement in exercise performance may be due to increased extrusion of H⁺ from the active muscle cell or conditions that lead to less H⁺ accumulation inside the cell (decreased La⁻ accumulation and decreased K⁺ loss from the cell). Many studies have reported increased [La⁻] and decreased [K⁺] in the extracellular (interstitial and plasma) space following intense exercise. This is supported by data showing less intracellular
acidification when extracellular acidosis is present [47]. It also sets up the possibility that muscle performance can be improved by generating more ATP from anaerobic glycolysis before a certain level of acidosis is reached [44].

Conclusions
The ingestion of NaHCO₃ before intense exercise attempts to alkalinize the blood and muscle in the hope that more H⁺ can be buffered and the metabolic acidosis with exercise can be tempered, leading to enhanced anaerobic energy production and exercise performance. Studies suggest that increases in blood [Na⁺] and [HCO₃⁻] with NaHCO₃ ingestion lead to a decreased blood [H⁺] but skeletal muscle [H⁺] is not altered. Several studies have reported performance increases in laboratory-based cycling tests and simulated running races in the field following NaHCO₃ ingestion where the contribution of anaerobic energy is high. However, many other studies have reported no benefits and a significant incidence of negative side effects following NaHCO₃ ingestion.

Summary
• Creatine supplementation for 4–6 days significantly increases muscle [creatine] and [phosphocreatine] and generally increases exercise performance during short-term, high-intensity, sprint-like exercise.
• The increase in muscle [creatine] following creatine supplementation increased the rate of muscle accretion that occurs with a resistance-training regimen in some investigations.
• Carnitine is required for LCFA transport into the mitochondria and buffering the acetyl-CoA increase during exercise. Oral carnitine supplementation does not increase muscle [carnitine], enhance VO₂max, or increase fat oxidation and endurance performance during sub-maximal exercise.
• Muscle carnitine content has been temporarily elevated by 10–20% with infusion-induced plasma hypercarnitinaemia and hyperinsulinaemia. These studies will be useful in assessing the importance of the muscle [carnitine] level for metabolic regulation during exercise.
• Skeletal muscle metabolic acidosis and related ion disturbances can limit performance during sporting events requiring high power outputs and substantial energy from substrate phosphorylation. Studies suggest that NaHCO₃ ingestion before exercise decreases blood [H⁺] but not skeletal muscle [H⁺].
• Many NaHCO₃ ingestion studies have reported performance increases in short-term, intense laboratory-based cycling tests and simulated running races while several others have reported no benefits. Negative side effects of ingesting NaHCO₃ are commonly reported.
References


