BIOCHEMISTRY OF BUFFERING CAPACITY AND INGESTION OF BUFFERS IN EXERCISE AND ATHLETIC PERFORMANCE

Bryan Saunders[1,2] (drbryansaunders@outlook.com)
Guilherme Giannini Artioli[1] (artioli@usp.br)
Eimear Dolan[1] (eimeardolan@usp.br)
Rebecca Louise Jones[3] (Rebecca.Jones@beds.ac.uk)
Joseph Matthews[4,5] (Joseph.Matthews@bcu.ac.uk)
Craig Sale[4] (craig.sale@ntu.ac.uk) *Primary contact author

1. Applied Physiology and Nutrition Research Group, School of Physical Education and Sport; Rheumatology Division; Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, BR, University of São Paulo, São Paulo, Brazil.
2. Institute of Orthopaedics and Traumatology, Faculty of Medicine FMUSP, University of São Paulo, Brazil.
3. Institute for Sport and Physical Activity Research, School of Sport Science and Physical Activity, University of Bedfordshire, Bedford, UK.
4. Musculoskeletal Physiology Research Group, Sport, Health and Performance Enhancement (SHAPE) Research Centre, School of Science & Technology, Nottingham Trent University, UK.
5. Research Centre for Life and Sport Sciences (CLaSS), School of Health and Life Sciences, Department of Sport and Exercise, Birmingham City University, Birmingham, UK.

ABSTRACT

Muscle fatigue is defined as the loss in force of power production in response to a muscle contraction and, during exercise, this results in the inability to sustain exercise at a given intensity. Although exercise-induced muscle fatigue is a complex and multifactorial phenomenon, it is accepted that hydrogen cation (H^+) accumulation in skeletal muscle during intense exercise, which causes a reduction in the intramuscular pH, disrupts muscle energetics and muscle contraction and is a major cause of peripheral fatigue. The resultant increase in H^+ within the skeletal muscle can negatively impact performance, particularly in those high-intensity events lasting between 1 and 10 min. The body has several intracellular and extracellular buffering systems that maintain pH homeostasis, although these may be exceeded during exercise. Nutritional interventions that might increase intracellular or extracellular buffering capacity could delay H^+ accumulation and ultimately fatigue. Beta-alanine, sodium bicarbonate, sodium citrate and calcium and sodium lactate are all buffering supplements with the capacity to increase intracellular or extracellular buffering capacity. Each of these supplements has been shown to improved exercise capacity and performance on numerous occasions, although several factors may modify their efficacy. The most promising of these are chronic supplementation with beta-alanine (to increase intramuscular buffering via an increase in muscle carnosine content) and acute supplementation with sodium bicarbonate (to increase extracellular buffering via an increase in circulating bicarbonate), which have been shown to be particularly effective for high-intensity exercise lasting 1-10 min in duration.

INTRODUCTION

Muscle fatigue is the loss in force or power production in response to muscle contraction (61). During exercise, this results in the inability to sustain exercise at a given intensity. It is widely accepted that exercise-induced muscle fatigue is a complex, multifactorial phenomenon caused by several mechanisms that can vary according to exercise type, intensity and duration. Both central (*i.e.*, arising in the central nervous system) and peripheral (*i.e.*, arising in skeletal muscle or the neuromuscular junction) events have been implicated in fatigue development (61).

Contracting the muscle at a high rate significantly increases the demand for adenosine-5'-triphosphate (ATP) turnover in order to meet the increased energy demand and maintain the rate of muscle contraction. Resynthesis of ATP is supported by the hydrolysis of phosphorylcreatine, glycolysis, and oxidative phosphorylation in mitochondria provided there is sufficient oxygen available. During high-intensity exercise, however, the rate of ATP hydrolysis can exceed the rate of ATP resynthesis provided by aerobic means, meaning that the shortfall in ATP must be met by the hydrolysis of phosphorylcreatine and anaerobic glycolysis (53). Meeting these energy demands comes at a cost, with anaerobic glycolysis being the primary metabolic process responsible for hydrogen cation (H^+) production in skeletal muscle and thus a reduction in the intramuscular pH, which is suggested to disrupt muscle energetics and muscle contraction (118). Specifically, intramuscular acidosis can inhibit the activity of key enzymes of energy metabolism, in particular phosphofructokinase, a key-regulator of glycolysis (120) and can inhibit the resynthesis of phosphorylcreatine (97). Acidosis can also disrupt skeletal muscle contractility, by reducing the sensitivity of the calcium-binding site of troponin to the Ca^{2+} ions (30, 118), and can directly interfere with actomyosin interactions by inhibiting the transition from the low- to the high-force state of the actin-myosin cross-bridge (25, 119). Since acidosis rapidly builds up during high-intensity exercise, it is assumed that it plays a major causative role in peripheral fatigue during this type of exercise (64).

Any strategy capable of delaying the increase in intramuscular H^+ concentration that accompanies high-intensity exercise has the potential to delay the onset of fatigue and is, thus, potentially ergogenic. The regulation of acid-base balance in the body is supported by several physiological mechanisms, including the actions of chemical and metabolic buffers that can alter the H^+ concentration in seconds, pulmonary ventilation that can excrete H^+ over the course of min and the action of the kidneys that can excrete H^+ over the longer-term. We will focus

on the chemical and metabolic buffers in the intracellular (*i.e.*, muscle) and extracellular (*i.e.*, blood) environments that support the control of intramuscular pH during exercise. In the following sections, we will focus on nutritional interventions that might have the potential to increase intracellular or extracellular buffering capacity, which could delay H^+ accumulation and fatigue.

BIOCHEMISTRY OF PH, FATIGUE AND INTRA/EXTRACELLULAR BUFFERING

Fundamental concepts

Hydrogen is the simplest element in nature, formed by a single positively charged proton and a single negatively charged electron. Single hydrogen atoms are, however, not common on earth, since they naturally combine with other elements to form molecules, such as the diatomic gas form of hydrogen (H_2) or water (H_2O). Water is essential for virtually all known forms of life, since all biochemical reactions require an aqueous medium to occur. Due to its molecular arrangement, in particular the hydrogen side of the molecule being positively charged and the oxygen side of the molecule being negatively charged, water becomes a polar molecule, with a high dielectric constant and it easily forms hydrogen bonds. These characteristics make water an excellent solvent, as the electric charges interact with numerous elements and molecules.

Water causes polar molecules to dissociate in ions, which are then dissolved to form a solution. In pure water, the only ions present are H^+ and OH^-, both in equal concentration. Since the concentration of positively and negatively charged ions are equal, pure water is neutral. Secondly, their concentrations are remarkably low. Thirdly, water neutrality is seen only when the concentration of both H^+ and OH^- is 10^{-7} M. Finally, the product of H^+ and OH^- concentration in pure water is 10^{-14}.

Since the concentration of ions in pure water is very low, it is convenient to use negative log; this avoids working with several decimal places. By calculating the negative log of the concentration of H^+ in pure water, we obtain pH, where "p" stands for the negative log of the hydrogen cation concentration in water. pH, therefore, is a measure of the hydrogen cation concentration in an aqueous solution, being expressed in a negative logarithmic scale. From the series of equations used above, we calculate that the pH of pure water is 7. Because H^+ concentration is equal to the concentration of OH^-, pOH is also 7. For that reason, 7 is the pH value that represents neutrality of an aqueous solution. When H^+ concentration increases, the solution becomes acidic, its pH decreases and its OH^- concentration decreases because of Le Chatelier's principle. Conversely, when OH^- concentration increases, the solution becomes alkaline (*i.e.*, pH increases) and its H^+ concentration decreases.

According to the Brønsted-Lowry definition of acids and bases, the term acid refers to a substance that can donate protons (*i.e.*, H^+), whilst the term base refers to a substance that is able to accept protons. Acids and bases tend to ionise in water, although the level of ionisation

depends upon the pH of the solution and the dissociation constant of the acid (Ka) or the base (Kb). Strong acids and bases completely dissociate in aqueous solutions, whereas weak acids and bases only partially dissociate. The dissociation of an acid (HA) can be expressed in the following simplified reaction:

$$HA \leftrightarrow H^+ + A^-$$

To identify the strength of the acid or, in other words, its ability to dissociate and donate protons, it is necessary to calculate the dissociation constant of the acid (Ka) using the formula:

$$K_a = \frac{[H^+] \times [A^-]}{[\mathrm{HA}]}$$

Since stronger acids tend to dissociate more than the weaker ones, the stronger the acid the higher its Ka value. Likewise, the weaker the acid, the lower its Ka value. Because the Ka values can differ by several orders of magnitude between weak and strong acids, it is convenient to work with their negative logarithms, thereby obtaining the pKa of an acid. Hence, the pKa of an acid represents the negative log of its dissociation constant, as exemplified in Table 1.

<<< Table 1 here >>>

From the dissociation equation above, one can calculate their log on both sides of the equation, as follows:

$$K_a = \frac{[H^+] \times [A^-]}{[\mathrm{HA}]}$$

$$\log K_a = \log\left(\frac{[H^+] \times [A^-]}{[\mathrm{HA}]}\right)$$

By splitting the log terms, we obtain:

$$\log K_a = \log[H^+] + \log\left(\frac{[A^-]}{[\mathrm{HA}]}\right)$$

If all terms are multiplied by -1, this give us:

$$-\log K_a = -\log[H^+] - \log\left(\frac{[A^-]}{[\mathrm{HA}]}\right)$$

Replacing the negative logs with their respective "p" terms, we obtain:

$$\mathrm{p}K_a = pH - \log\left(\frac{[A^-]}{[\mathrm{HA}]}\right)$$

Or:

$$pH = \mathrm{p}K_a + \log\left(\frac{[A^-]}{[\mathrm{HA}]}\right)$$

This is the Henderson-Hasselbalch equation and it is important since it relates pH, pKa and the percentage of dissociation of an acid (or a base). From this equation, for example, we can see that an acid is 50% in its undissociated form and 50% in its dissociated form when the pH of the medium is equal to its pKa. Thus, the pKa of an acid can also be interpreted as the pH of the solution at which this acid will be 50% dissociated and 50% undissociated.

Physiological pH buffering systems

Since H^+ and OH^- ions are highly reactive, any shift in pH neutrality, either to the acid or the alkali side, can have a profound impact on key physiological processes, such as enzyme activity and protein structure and function. Most cells and physiological systems operate with their pH tightly regulated and close to neutrality. Such a fine tune of pH is achieved thanks to several buffering systems that prevent abrupt changes in pH, as would occur when small amounts of acid or alkali are added to an aqueous solution with no buffering systems (Figure 1, Panel A). In a buffered system, the addition of acid will not cause such a sudden drop in pH, at least within certain pH limits (Figure 1, Panel B).

<<< Figure 1 here >>>

Figure 1. Schematic representation of titration curves of pure water (panel A) and a buffered aqueous solution (panel B). In pure water, where there is no buffering system, the addition of small amounts of acid results in a large reduction in pH, whilst in a buffered system, there is a zone where the addition of large amounts of acid does not result in a reduced pH. The zone of effectiveness refers to the pH range around the pKa of that particular buffer, thereby varying according to the buffering agent.

In most animals, both intracellular and extracellular pH are tightly regulated, although the physiological pH range varies slightly between blood and the intracellular medium. In blood, the pH is slightly alkaline (~7.4) whereas in the intracellular medium, pH is typically close to

neutrality (~7.0), although this may vary within cellular compartments or between cell types. As such, the buffering systems operating within the blood are different from those operating inside cells. In blood, the most important buffering system is bicarbonate (HCO_3^-), which works in equilibrium with carbonic acid (H_2CO_3), as depicted in the simplified reaction below.

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

When there is an increase in H^+ concentration in blood (*i.e.*, acidosis), the reaction is shifted to the right, meaning that the neutralisation of H^+ by HCO_3^- increases, thereby increasing the formation of CO_2 and reducing HCO_3^- concentration. The resulting CO_2 then stimulates an increase in ventilation, through which CO_2 is eliminated. This condition is known as metabolic acidosis and occurs during high-intensity exercise. Alternatively, when there is an increase in CO_2 concentration, the reaction $H_2CO_3 \leftrightarrow CO_2 + H_2O$ is shifted to the right, thereby reducing the concentration of H_2CO_3 in relation to the HCO_3^-. This condition is known as respiratory alkalosis, and it is easily observable when an individual hyperventilates. Another way to induce blood alkalosis is through an increase in HCO_3^- concentration, a condition known as metabolic alkalosis and inducible via the ingestion of nutritional supplements, as discussed in this chapter.

Inside cells, the equilibrium between the protonated and non-protonated forms of dihydrogen phosphate ($H_2PO_4^-$) is one system that can prevent changes in intracellular pH when the acid or alkali load increases, as shown in the reaction below. Another important buffer operating inside cells is the protein system. This system relies on the ability of the amino acid residues to ionise and accept or donate H^+ within the physiological pH range. Because all amino acids have an acid group ($COOH \leftrightarrow COO^-$) and a base group ($NH_2 \leftrightarrow NH_3^+$) that have very low and high pKa's (~2 and ~10), they cannot effectively buffer pH changes within the physiological pH range; therefore, the buffering activity of an amino acid is dependent upon two characteristics of its side-chain: 1) whether it is ionisable and 2) whether its pKa is close to the physiological pH. As shown in Table 2, histidine is the sole amino acid that can effectively work as a pH buffer in the intracellular medium where pH is close to neutrality. The pKa of amino acids can change when they bind to and interact with other amino acids. Carnosine, a dipeptide formed by histidine and β-alanine, is a good example, as the pKa of histidine changes from 6.0 to 6.9 when it is bound with β-alanine. This has important implications for pH regulation during exercise.

<<< Table 2 here; Source: (15) >>>

The body has several intracellular and extracellular physiological buffers that can accept or release H^+ to prevent pH changes. This is particularly important during high-intensity exercise, which causes an accumulation of H^+ that can lead to fatigue and negatively impact performance. In muscle, physicochemical buffers such as organic and inorganic phosphates, bicarbonate anions and histidine containing dipeptides (*e.g.*, carnosine) are the primary mediators of pH homeostasis, while H^+ are also actively and passively transported out of the muscle into the blood mediated by transport systems. Therefore, a nutritional intervention designed to increase buffering capacity may thus be of benefit to exercise performance. The following sections will detail the available evidence on nutritional supplements that have the potential to increase intracellular or extracellular buffering capacity.

BETA-ALANINE SUPPLEMENTATION

Carnosine (comprising β-alanine and L-histidine) is abundant in skeletal muscle, and is purported to have many therapeutic (3) and ergogenic (99) properties. Potential mechanisms through which these influences occur include the reduction of reactive oxygen or nitrogen species (13), anti-glycation (51) and the regulation of calcium transients and sensitivity (35). While it is possible that some, or all, of these functions contribute toward carnosine's ergogenic and therapeutic properties, the strongest line of evidence supports an important role for carnosine as an intracellular physicochemical buffer (28). This action is possible because the pKa of carnosine (and more specifically of its imidazole ring; 6.83 (7)) renders it ideally placed to act as a pH buffer across the pH transit range of the intramuscular environment, which has been reported to reduce from approximately 7.1 at rest to between 6.5 and 6.1 following exhaustive high-intensity exercise (88, 98).

The contribution of carnosine toward intracellular buffering capacity is dependent upon its content and, as such, it is desirable for individuals with a high requirement for intracellular buffering (*e.g.,* athletes who regularly undertake high-intensity exercise) to augment their supply (Figure 2). Beta-alanine is the rate-limiting amino acid for carnosine synthesis (45), and supplementation with this amino acid increases carnosine content (104) and is ergogenic in certain situations (102). These properties have led to its application as one of the most widely-used sports supplements available today, and justifies its inclusion as one of 5 effective sport-supplements indicated for use by various international organisations, including the International Olympic Committee (68).

<<< Figure 2 here >>>

Figure 2. Overview of beta-alanine supplementation to increase muscle buffering capacity during high-intensity exercise.

Supplementation strategies

The first study to demonstrate that beta-alanine supplementation could increase muscle carnosine content reported that beta-alanine ingestion of 3.2–5.2 $g \cdot day^{-1}$ (mean) for 4 weeks (equating to 89.6–145.6 g total beta-alanine) led to muscle carnosine increases of approximately 40–65% (45). Further independent studies have since confirmed these findings across a range of doses (1.6–6.4 $g \cdot day^{-1}$), durations (2-24 weeks) and analysis techniques (HPLC and ^{1}H-MRS) (4, 9, 12, 49, 104).

It seems that the main determinant of carnosine content in response to supplementation is the total amount ingested. Church et al. (19) reported equivalent increases in muscle carnosine when 168 g of carnosine was ingested, either as 12 $g \cdot day^{-1}$ for 2 weeks or as 6 $g \cdot day^{-1}$ for 4 weeks. Similarly, Stellingwerff et al. (116) reported a two-fold greater increase in muscle carnosine content when participants ingested 3.2 as opposed to 1.6 $g \cdot day^{-1}$ for 4 weeks. The upper limit of carnosine content attainable via beta-alanine supplementation is currently unknown. The longest trial conducted to date supplemented 6.4 $g \cdot day^{-1}$ beta-alanine for 24 weeks, with muscle carnosine content measurements taken every 4 weeks throughout the investigation (104). The greatest increases were shown in the first 4-8 weeks of supplementation, although muscle carnosine content continued to increase throughout the 24 weeks, with some individuals continuing to show increases at the final 24-week collection point, demonstrating that they may not yet have reached saturation.

Effects on exercise performance

Hill and colleagues (49) first showed that a beta-alanine induced increase in muscle carnosine could improve high-intensity exercise capacity. Since then, numerous studies have investigated the influence of beta-alanine supplementation on a wide range of exercise tests and performance parameters. Meta-analytical data showed a significant main effect of beta-alanine supplementation on exercise outcomes (0.18; 95% CI 0.08–0.28) (102). Importantly, the authors also conducted a meta-regression to identify whether different factors – including exercise duration; type (capacity-based tests conducted to exhaustion, or performance-based tests that used a set task); mode (whole body or isolated limb) and mode 2 (intermittent or continuous) – influenced this main effect. In line with an important role of muscle carnosine in delaying fatigue due to increased intracellular buffering capacity, the meta-regression indicated that beta-alanine supplementation exerted its greatest influence in capacity-based tests lasting 30 s to 10 min. In contrast, shorter (0–30 s) and longer (>10 min) tests were unlikely to be improved by beta-alanine supplementation, probably because pH changes have a smaller contribution to fatigue in very short, or more prolonged, exercise tests. The effect of beta-alanine was smaller for trained compared to non-trained individuals, although Painelli et al. (87) directly compared the efficacy of beta-alanine supplementation on training status comparing a trained and non-trained population and showed it to be equally effective in both groups. Importantly, any small gains may translate into worthwhile improvements in applied settings (*i.e.*, competition) for competitive athletes.

The influence of beta-alanine supplementation on performance in intermittent tasks such as repeated sprint ability and resistance exercise has been widely studied; acidosis is likely to contribute, at least in part, to performance in these activities (115, 122). Theoretically, it makes sense that beta-alanine supplementation would be most efficacious toward the latter stages of repeated, intense efforts, when acidosis may negatively impact continued ATP regeneration and directly hinder muscle contractile properties (37). Repeated sprint ability is important for a wide range of intermittent team sports, such as football, hockey, rugby and basketball. Longer duration repeated efforts, such as repeated upper- (123) and lower- (87) body Wingates or YoYo performance (108) are more amenable to beta-alanine supplementation than are shorter duration repeated efforts (32, 52, 105, 106, 121).

The effects of beta-alanine supplementation on strength and resistance-based exercise outcomes are equivocal. Hoffman et al. (52) showed improved repeated isotonic endurance performance with beta-alanine, although no such effect on similar exercise outcomes has been shown by others (5, 6). Mixed results have also been reported on the effects of beta-alanine on isometric hold endurance, with studies showing an improvement (6, 100) or no influence (27, 55). Such isometric holds result in reduced blood flow to the muscle and generate a hypoxic environment, increasing reliance upon anaerobic metabolism. The muscle essentially functions as a closed unit during these holds, meaning that the ability to remove H^+ is also limited, further exacerbating the ability of the muscle to regulate pH. Insufficient evidence is currently available to make a clear conclusion on the influence of beta-alanine supplementation on strength and resistance exercise outcomes.

The evidence described above is based upon isolated beta-alanine supplementation protocols for acute exercise, but perhaps of equal importance to the athlete is the potential for an enhanced ability to perform high-intensity exercise to contribute to a higher training intensity, which would augment training adaptations. A number of studies have investigated the influence of beta-alanine supplementation alongside a high intensity interval training (HIIT) programme and the majority of these showed no added effect of beta-alanine supplementation with training when compared to training alone (20, 113, 126). An important point to consider here, however, is that beta-alanine supplementation typically takes at least 2-3 weeks to show measurable muscle carnosine increases (116), and the aforementioned investigations lasted 6 weeks, meaning that these would have been less likely to show benefits of beta-alanine

supplementation from the outset. Supporting this, Smith et al. (114) reported comparable exercise improvements following HIIT with beta-alanine and placebo for the first 3 weeks of the training protocol, but superior influences in the beta-alanine group after 6 weeks. Similarly, Bellinger and Minihan (8) pre-supplemented a group of cyclists with 6.4 $g \cdot day^{-1}$ of beta-alanine for 4 weeks prior to a 5-week sprint training program and showed a beneficial influence of supplementation and training. Thus, beta-alanine supplementation could well have the capacity to improve exercise training outcomes, but supplementation prior to the implementation of the training programme is obviously required to ensure these benefits are achieved.

Side-effects

The longest supplementation study to date showed that 24-weeks of supplementation at 6.4 $g \cdot day^{-1}$ did not change clinical markers of health in healthy individuals (103). The available evidence indicates that beta-alanine supplementation (within the doses and durations that have been scientifically investigated) is safe (29). The primary side-effect experienced is paraesthesia, which has been described as an uncomfortable prickly sensation on the skin. Paraesthesia most likely occurs due to the binding of beta-alanine to the peripheral neuronal receptor MrgprD (66). Although many individuals consider it an unpleasant sensation, there is no evidence to indicate that it is harmful. The occurrence and intensity of paraesthesia is dose-related and closely relates to the time and peak of blood beta-alanine concentration (45). Accordingly, strategies to slow the time or extent of peak blood beta-alanine, such as splitting the desired dose throughout the day (45) or using a slow-release capsule (26) have been reported to effectively reduce the occurrence or intensity of paraesthesia symptoms.

Animal studies show that beta-alanine supplementation may reduce intracellular taurine content, because the increase in beta-alanine availability increases competition for their shared transporter, TauT. Despite this, 24-weeks of 6.4 $g \cdot day^{-1}$ beta-alanine did not affect the taurine pool in muscle (103). A recent systematic risk assessment of beta-alanine supplementation meta-analysed all available data and showed no effect of beta-alanine supplementation on muscle taurine content in humans (29). The discrepant findings between humans and animals likely relates to the very large difference in dosing protocols used, with animal studies typically employing doses that are 38–56-fold larger than those used in human studies. Another theoretical concern of beta-alanine supplementation that has been raised is that it may reduce intracellular free histidine content (12), given that histidine is also required to synthesise carnosine. But, the same meta-analysis of human data indicates that this is not the case, and

that beta-alanine supplementation (within doses investigated) does not reduce free histidine content. As such, the available evidence indicates that beta-alanine supplementation is a safe ergogenic aid.

SODIUM BICARBONATE SUPPLEMENTATION

Normal resting blood bicarbonate concentrations range between 23-27 mmol·L^{-1} (67). Sodium bicarbonate is a buffering agent capable of inducing alkalosis via increases in blood pH and bicarbonate (21, 60). This aids in the maintenance of muscle acid-base balance during exercise, increasing the efflux of H^+ from the contracting muscle (59), forming carbonic acid and allowing further buffering by the respiratory system (Figure 3). Sodium bicarbonate is another supplement included as one of the 5 sport-supplements that have sufficient evidence to support their use by the International Olympic Committee (68).

<<< Figure 3 here >>>

Figure 3. Overview of supplementation with extracellular buffers (sodium bicarbonate, sodium citrate, calcium lactate and sodium lactate) to increase extracellular buffering capacity during high-intensity exercise.

Supplementation strategies

Available evidence suggests that, to gain a potential or almost certain improvement in exercise performance, an increase in blood bicarbonate concentration in excess of +5 and +6 mmol·L^{-1} from baseline is required (17). Acute ingestion of 0.3 g·kg^{-1} body mass (BM), the most commonly ingested dose, is sufficient in increasing absolute blood bicarbonate concentrations to these levels (40, 56, 72). Doses above 0.3 g·kg^{-1}BM have demonstrated no additional performance benefits despite greater increases in bicarbonate (72) while a 0.1 g·kg^{-1}BM dose is insufficient in raising circulating blood bicarbonate concentrations >6 mmol·L^{-1} (56) and appears not to improve exercise outcomes (72). Individual variability in blood bicarbonate responses following 0.2 g·kg^{-1}BM (56) could explain why the exercise benefits with this dose are contrasting (21, 60, 72, 96). The maximal absolute increases in circulating bicarbonate following ingestion of 0.2 and 0.3 g·kg^{-1}BM are reported as being similar (44), and have comparable exercise effects. This suggests that it is useful to time supplement ingestion so that exercise coincides with peak alkalosis in order to optimise sodium bicarbonate supplementation at lower doses. Further work is necessary to clarify these claims.

It appears logical to suggest that the greatest ergogenic effect following sodium bicarbonate ingestion would occur at peak alkalosis. The most commonly employed ingestion strategy is to consume sodium bicarbonate at a standardised timepoint, 60-180 min prior to exercise (33, 92, 94, 112) albeit these data have been challenged (18, 44, 56, 111). Consumption of 0.3 $g \cdot kg^{-1}$BM of sodium bicarbonate results in peak blood bicarbonate concentration between 10 (75) and 180 min (56) following ingestion. Therefore, rather than following generalised approaches, individualised sodium bicarbonate ingestion strategies designed to align peak alkalosis with the onset of exercise performance may be more effective. Individualised strategies have demonstrated high repeatability for time-to-peak blood bicarbonate and pH responses (43). Individuals adopting this approach are, however, required to have prior knowledge of blood bicarbonate responses together with the flexibility to manipulate the timeframe leading up to performance. This may be difficult for athletes engaged in repeated events throughout the day or those that have strict schedules. More recent data suggests, however, that individualising supplementation to a solitary peak timepoint is unnecessary, and that there is a long-lasting ergogenic window of opportunity with sodium bicarbonate lasting approximately 3 h from 60-min post-ingestion (23). Those with a short timeframe to supplement prior to exercise should consider ingesting a lower dose, since 0.1-0.3 $g \cdot kg^{-1}$BM showed similar blood bicarbonate responses in the initial 30 min post-ingestion (56). Serial sodium bicarbonate ingestion across several days is also a purported method by which to maintain chronically elevated blood bicarbonate levels (71). This serial dosing strategy can lead to exercise improvements (34, 82), although not all studies show this strategy to be effective (58). Individuals should experiment with different supplementation strategies to determine which one works best for them, although 0.3 $g \cdot kg^{-1}$BM ingested 60-180 min before exercise appears to be beneficial under most circumstances.

Effects on exercise performance

To gain an ergogenic effect following sodium bicarbonate ingestion, both the duration and the intensity of the exercise should be considered. Sodium bicarbonate increases buffering capacity; therefore, performance benefits are only likely to be reported when exercise is limited by increases in H^+ accumulation. High-intensity exercise of short duration, such as those lasting 10-30 s, have demonstrated no improvements following sodium bicarbonate ingestion (73), while most studies report no improvements during endurance exercise (39, 81, 117). A 1-10 min exercise duration is the most likely to be improved by sodium bicarbonate (40, 72, 73),

although exercise intensity likely also plays an important role (48). Repeated sprint exercise, common during team sports, has been shown to be limited by H^+ buffering capacity (93). Intermittent protocols such as these (*i.e.*, repeated sprint exercise) do appear particularly susceptible to improvements with sodium bicarbonate supplementation (10, 11, 63, 75). Similar to beta-alanine, the ergogenic effects of sodium bicarbonate appear reduced in trained individuals (90), but its application in a competitive setting may lead to worthwhile changes in performance.

The effect of sodium bicarbonate between individuals appears variable, with some individuals improving performance while others do not, despite similar increases in blood variables (107). Within-individual blood responses following ingestion of sodium bicarbonate appear consistent, although consistency of the ergogenic effect on exercise performance is disputed (40, 42). This, however, may be due to the contrasting nature of the populations employed; inconsistent exercise results have been shown with non-trained (40), but not trained (42), individuals. There is the possibility that inconsistent exercise results are due to variable blood responses between individuals, particularly in response to ingestion at a standardised timepoint prior to exercise, since not all individuals may have experienced sufficient alkalosis to influence performance. This has led to studies employing time-to-peak bicarbonate protocols to coincide exercise with the greatest changes in circulating bicarbonate. The only two studies to date that have employed this tactic have shown positive results (44, 75), although further work is necessary to elucidate whether this approach elicits greater and more consistent gains for exercise performance and capacity.

Most sodium bicarbonate research has focused upon acute ingestion to improve exercise performance, although a few studies have explored the influence of serial ingestion in conjunction with high-intensity interval training with conflicting results. Evidence has shown greater beneficial effects of combined training with supplementation than training alone on aerobic and anaerobic measures (36, 57, 127), although not all agree (31). There is a growing body of evidence that sodium bicarbonate may be effective for exercise performed in extreme environments, such as hypoxia (24, 41, 106) and the heat (80). These extreme environmental conditions result in greater than normal lactate and H^+ accumulation and are, thus, likely to be extremely susceptible to increased buffering capacity; suggesting a further avenue for research.

Side-effects

Upon entering the stomach, the bicarbonate neutralises large quantities of the H^+ present within the stomach's gastric juices producing carbon dioxide, which can cause abdominal pain, flatulence, nausea, diarrhoea and vomiting (14). The intensity and duration of these symptoms are intrinsically linked to the dose ingested, with greater discomfort experienced with increasing doses (72). It is important to determine the impact these side-effects may have, since they have the potential to influence an individual's performance and potentially the overall outcome of the investigation. Saunders et al. (107) only showed improvements in high-intensity cycling capacity when individuals suffering from gastrointestinal distress were removed from the analysis. Several strategies have been developed to avoid these side-effects, including split-dose strategies (101, 107), multiday consumption (71, 79) or carbohydrate ingestion alongside supplementation (17). Strategies that minimise bicarbonate losses in the stomach have been suggested to be a viable method to minimise side-effects (22); this may include delayed-release (50) or enteric coated (14) capsules, although research on this topic is currently underexplored. It is also important to note that frequent or chronic sodium bicarbonate supplementation will lead to a chronically increased sodium load for the body, which could impact kidney function, although no study has determined this directly.

SODIUM CITRATE

Research into the use of sodium citrate as an ergogenic aid began over 30 years ago (89). It acts as an alkalising agent, since the utilisation of protons during the oxidation of citrate indirectly generates bicarbonate, leading to an increased buffering capacity in a similar manner to sodium bicarbonate (64). Following initial positive findings, subsequent studies suggested sodium citrate had low efficacy and it received less attention than comparable buffering agents such as sodium bicarbonate. There has been a resurgence in its popularity due to a series of recent findings and the possibility that sodium citrate carries a lower incidence of GI-related side-effects than sodium bicarbonate (124).

Supplementation Strategies

Sodium citrate is supplemented in powder or capsule form and ingested acutely prior to exercise. Two key factors that may alter its efficacy are the timing and relative dose of supplementation, which should be structured to elicit the greatest alkalotic effect at the onset of exercise. Ingestion consistently leads to an increase in plasma bicarbonate, with several studies showing an increase in excess of the theoretical potential ($\geq$5 mmol·L^{-1}) and certain ($\geq$6 mmol·L^{-1}) ergogenic thresholds (46). McNaughton (74) first showed a dose-response to

sodium citrate supplementation for intakes ranging from 0.1 to 0.5 g·kg^{-1}BM; ninety min post-ingestion, exercise performance, blood pH and bicarbonate were greatest with the highest 0.5 g·kg^{-1}BM dose. The two lowest doses, 0.1 and 0.2 g·kg^{-1}BM, did not result in an ergogenic effect. As a consequence of these data, most studies have adopted 0.3 g·kg^{-1}BM or 0.5 g·kg^{-1}BM as the experimental treatment dose (70, 83, 84, 110).

Urwin and colleagues (124) investigated the time course of blood response following higher doses of sodium citrate, although results confirmed 0.5 g·kg^{-1}BM as the most effective; 0.7 g·kg^{-1}BM and 0.9 g·kg^{-1}BM led to worse side-effects without further changes in blood pH or bicarbonate. Their results did, however, suggest that the standardised ingestion time used in most studies (*i.e.*, 90 min pre-exercise) may be sub-optimal. Blood alkalosis peaked between 180- and 215-min post-ingestion, suggesting that sodium citrate should be taken a minimum of 180 min pre-exercise. This recent evidence may explain some of the equivocal findings in the research (86), since the greatest chance of an improvement in exercise performance is likely to come from supplementation strategies that maximise increases in blood pH and bicarbonate prior to exercise.

Effects on Exercise Performance

Parry-Billings and MacLaren (89) showed that sodium citrate had no effect on anaerobic power and capacity, with McNaughton (74) being the first to show a beneficial effect of sodium citrate supplementation on total work and peak power output during a maximal one-minute cycle ergometer sprint. The degree of performance enhancement increased with each ascending dose and increase in blood alkalosis (74). A subsequent study supported the use of sodium citrate supplementation to enhance performance for maximal tasks lasting from two to four min, but not for tasks ≤30 seconds in duration (70), consistent with its role as an extracellular pH buffer. Despite these favourable results, meta-analytical data of sodium citrate supplementation showed evidence to be equivocal (16). Pooled data from 13 studies showed an unclear effect on performance (0.0±1.3% change in mean power), which was not modified by sex, athletic status, or the supplement dose. The lack of effect occurred despite a similar temporal response of blood pH and bicarbonate to that of sodium bicarbonate supplementation. When standardised to an equimolar dose, sodium citrate appears less effective than sodium bicarbonate at improving exercise performance: 1% vs. 6.3% improvement in high-intensity running to exhaustion (125).

These findings question the efficacy and mechanism of action of sodium citrate. A possible explanation is that an inhibitory effect of increased intracellular citrate counteracts the increase in extracellular buffering capacity (62). Citrate can allosterically inhibit the rate-limiting glycolytic enzyme, phosphofructokinase, and thus reduce adenosine triphosphate production. A further issue could be the timing of ingestion, since most studies included in the meta-analysis supplemented sodium citrate 90- to 120-min prior to exercise (16). As discussed, this may be a sub-optimal strategy as it does not allow for peak blood alkalosis and coincides with greater side-effects (124). Thus, improvements in exercise performance may be more apparent with a longer period between sodium citrate ingestion and the start of the task, but this remains to be experimentally confirmed.

Side-effects

There is a perceived lower risk of GI discomfort compared to sodium bicarbonate (91, 95), although side-effects still occur with sodium citrate. The most common symptoms include stomach cramps, bloating, nausea, vomiting, urge to defecate, diarrhoea, thirst and headache (84, 109, 110); essentially the same side-effects as sodium bicarbonate. Early studies reported no side effects from sodium citrate doses ranging from 0.1 to 0.5 $g \cdot kg^{-1}$BM (62, 74, 89), although these investigations failed to adequately record the incidence and severity of side effects, meaning that mild symptoms went unnoticed. Later studies reported side-effects with doses of 0.5 $g \cdot kg^{-1}$BM (83, 84, 110), but GI distress was not experienced by volunteers in all studies (125). Symptom prevalence and severity increase in a dose-dependent manner for intakes of 0.5, 0.7 and 0.9 $g \cdot kg^{-1}$BM (124). Key moderators of these effects appear to be the volume of fluid supplied with the supplement and the time permitted to consume the fluid; concentrated solutions with a higher osmolality are more likely to result in GI distress (65). Higher doses potentiate these symptoms (124) and lower or staggered doses may reduce symptom prevalence and/or severity (74). Side effects may also have an ergolytic effect on exercise, particularly if sodium citrate is ingested 60 to 90 min pre-exercise, which means that individuals would perform exercise at the moment of the highest risk of GI distress and without reaching peak blood alkalosis (124).

SODIUM AND CALCIUM LACTATE

Lactate supplementation has been purported as a strategy for increasing extracellular buffering capacity. Following ingestion of sodium or calcium lactate, the lactate is absorbed in the intestine, preferentially in the jejunum (47), entering the blood stream and increased blood

lactate concentration. The lactate can subsequently be oxidised or used as a metabolic substrate in gluconeogenesis (69, 76), processes that consume a H^+, subsequently altering acid-base balance. The increased lactate can also be taken up by the tissue for oxidation (54), or by hepatocytes for conversion into glucose (1). The transport of lactate into tissues is facilitated by the monocarboxylate transporters 1 and 4, which co-transport with H^+ in a 1:1 ratio (59), thereby resulting in a net loss of H^+ in blood, increasing blood pH and sparing blood bicarbonate, which may be useful during high-intensity exercise.

Supplementation strategies

Lactate is commonly provided in doses between 120 and 300 mg·kg^{-1}BM; one study employed a dose as low as ~14 mg·kg^{-1}BM (81), although they showed no changes in blood variables, suggesting that this low dose is incapable of increasing buffering capacity, and increases in circulating bicarbonate and blood pH were modest at best. Mean bicarbonate increases of approximately +3 mmol·L^{-1} have been shown after ingesting 250 ml of an 80% polylactate solution (38) and 120 mg·kg^{-1}BM in gelatine capsules (78); this is approximately half the increase usually shown with a 0.3 g·kg^{-1}BM dose of sodium bicarbonate (46). De Salles Painelli et al. (85) aimed to determine the optimal lactate dose and timing for peak increases in blood pH and bicarbonate using a low (150 mg·kg^{-1}BM) and high (300 mg·kg^{-1}BM) dose of calcium lactate. Both doses only resulted in increased bicarbonate concentrations of around +2 mmol·L^{-1}, with similarly small increases in pH, and peak values occurred 60-90 min following supplement ingestion. Morris et al. (77) showed increases of approximately +2.5 mmol·L^{-1} 70-min post ingestion of 120 and 300 mg·kg^{-1}BM. Five days of calcium lactate supplementation at 500 mg·kg^{-1}·day^{-1} did not result in blood alkalosis, suggesting that a chronic supplementation strategy is inefficient for increasing buffering capacity (82). Acute lactate doses of between 120 and 300 mg·kg^{-1}BM 60-90 min prior to exercise appear most likely to increase buffering capacity, albeit more modestly than sodium bicarbonate or sodium citrate.

Effects on exercise performance

Morris et al. (78) showed a 17% improvement in exercise tolerance during a high-intensity cycling capacity test to exhaustion at 100% of maximal power output with 120 mg·kg^{-1}BM calcium lactate; the same group showed improvements (+14 and +26%) in the same high-intensity exercise test following two doses of 120 and 300 mg·kg^{-1}BM of calcium lactate (77). These impressive gains are not consistent within the literature, with further studies failing to show any efficacy of this supplement (81, 82). Methodological differences may explain the

lack of an effect of lactate on performance in these studies, such as a very low dose unlikely to increase buffering capacity (81) and chronic supplementation which resulted in no increases in circulating bicarbonate (82). However, performance during the 3-bout upper-body Wingate test was not improved with either 150 or 300 mg·kg^{-1}BM of acute calcium lactate ingestion (85). Since this exercise test is susceptible to changes in buffering capacity with sodium bicarbonate and beta-alanine (2, 123), these findings cast doubt on the efficacy of lactate as an ergogenic aid. One study compared the efficacy of sodium lactate with sodium bicarbonate and sodium citrate in male endurance runners. A 400 mg·kg^{-1}BM dose of sodium lactate 90-min prior to a run to exhaustion (at maximum effort to elicit fatigue in 1–2 min) improved performance by 1.7%, which was higher than the improvement shown with sodium citrate (0.5%) although lower than that with sodium bicarbonate (2.7%) (125).

Side-effects

Only two studies have reported any side-effects with acute lactate supplementation, volunteers experiencing similar levels of belching and flatulence following 150 and 300 mg·kg^{-1}BM of calcium lactate (85) and very low levels of sickness and stomach ache with 400 mg·kg^{-1}BM (125). The associated side-effects with lactate supplementation appear to be minor and unlikely to harm exercise performance.

OUTSTANDING QUESTIONS AND DIRECTIONS FOR FUTURE RESEARCH

- The greatest possible increases in muscle carnosine with beta-alanine supplementation are currently unknown and are worth determining to see if concomitant changes in exercise capacity and performance can also be maximised.
- The effects of beta-alanine for resistance and strength-based exercise is unclear. Further research using intensive protocols, those commonly used in real-life situations, are required to clarify its potential as an ergogenic aid for resistance athletes.
- The efficacy of sodium citrate and sodium/calcium lactate for exercise performance relative to sodium bicarbonate (considered the most effective of these extracellular buffers) needs to be further investigated. This will allow determination of whether supplementation with these alternative products is useful.
- The optimal timing of sodium bicarbonate (and sodium citrate) to induce the greatest alkalosis and minimal side-effects at the moment exercise begins is currently suggested

but not strongly demonstrated. Studies should determine whether these claims are substantiated.

- Alternative supplementation strategies to reduce side-effects with extracellular buffers warrant future investigation. This may include gastro-resistant capsules, split-dose strategies and lower doses with adapted timing of ingestion.
- More work is necessary to determine if any of these buffering supplements are more effective for exercise performed in extreme environmental conditions that result in greater than normal H^+ accumulation, such as hypoxia or heat.

SUMMARY AND CONCLUSIONS

Intense exercise challenges skeletal muscle homeostasis, partly through the production of lactic acid that occurs when the rate of glycolysis outstrips the rate of pyruvate oxidation. The resultant increase in H^+ within the skeletal muscle contributes to fatigue, particularly in those high-intensity events lasting between 1 and 10 min. The action of buffers in the skeletal muscle can help to protect against the rate of H^+ accumulation. Over time, however, H^+ will still accumulate and they must be transported out of the muscle and into the blood, resulting in reduced blood pH. One possible means to delay the onset of fatigue during this type of exercise is to increase the intracellular and/or extracellular buffering capacity. Several dietary supplements have some potential to achieve this; the most promising being chronic supplementation with beta-alanine (to increase intramuscular buffering via an increase in muscle carnosine content) and acute supplementation with sodium bicarbonate (to increase extracellular buffering via an increase in circulating bicarbonate). Both supplements have been listed by the International Olympic Committee as sport-supplements where there is sufficient evidence to substantiate its recommendation for use to improve exercise performance (68).

REFERENCES

1. **Adeva-Andany MM, Perez-Felpete N, Fernandez-Fernandez C, Donapetry-Garcia C, and Pazos-Garcia C**. Liver glucose metabolism in humans. *Bioscience reports* 36: 2016.
2. **Artioli GG, Gualano B, Coelho DF, Benatti FB, Galley AW, and Lancha AH**. Does sodium-bicarbonate ingestion improve simulated judo performance? *Int J Sport Nutr Exerc Metab* 17: 206-217, 2007.
3. **Artioli GG, Sale C, and Jones RL**. Carnosine in health and disease. *Eur J Sport Sci* 1-10, 2018.
4. **Baguet A, Bourgois J, Vanhee L, Achten E, and Derave W**. Important role of muscle carnosine in rowing performance. *J Appl Physiol (1985)* 109: 1096-1101, 2010.
5. **Bailey CH, Signorile JF, Perry AC, Jacobs KA, and Myers ND**. Beta-Alanine Does Not Enhance the Effects of Resistance Training in Older Adults. *Journal of dietary supplements* 15: 860-870, 2018.
6. **Bassinello D, de Salles Painelli V, Dolan E, Lixandrao M, Cajueiro M, de Capitani M, Saunders B, Sale C, Artioli GG, Gualano B, and Roschel H**. Beta-alanine supplementation improves isometric, but not isotonic or isokinetic strength endurance in recreationally strength-trained young men. *Amino Acids* 2018.
7. **Bate-Smith EC**. The buffering of muscle in rigor; protein, phosphate and carnosine. *J Physiol* 92: 336-343, 1938.
8. **Bellinger PM, and Minahan CL**. Additive Benefits of beta-Alanine Supplementation and Sprint-Interval Training. *Med Sci Sports Exerc* 48: 2417-2425, 2016.
9. **Bex T, Chung W, Baguet A, Stegen S, Stautemas J, Achten E, and Derave W**. Muscle carnosine loading by beta-alanine supplementation is more pronounced in trained vs. untrained muscles. *J Appl Physiol* 116: 204-209, 2014.
10. **Bishop D, and Claudius B**. Effects of induced metabolic alkalosis on prolonged intermittent-sprint performance. *Med Sci Sports Exerc* 37: 759-767, 2005.
11. **Bishop D, Edge J, Davis C, and Goodman C**. Induced metabolic alkalosis affects muscle metabolism and repeated-sprint ability. *Med Sci Sports Exerc* 36: 807-813, 2004.
12. **Blancquaert L, Everaert I, Missinne M, Baguet A, Stegen S, Volkaert A, Petrovic M, Vervaet C, Achten E, M DEM, S DEH, and Derave W**. Effects of Histidine and beta-alanine Supplementation on Human Muscle Carnosine Storage. *Med Sci Sports Exerc* 49: 602-609, 2017.
13. **Boldyrev AA, Stvolinsky SL, Fedorova TN, and Suslina ZA**. Carnosine as a natural antioxidant and geroprotector: from molecular mechanisms to clinical trials. *Rejuvenation research* 13: 156-158, 2010.
14. **Breitkreutz J, Gan TG, Schneider B, and Kalisch P**. Enteric-coated solid dosage forms containing sodium bicarbonate as a drug substance: an exception from the rule? *The Journal of pharmacy and pharmacology* 59: 59-65, 2007.
15. **Butterworth PJ**. Lehninger: principles of biochemistry (4th edn) D. L. Nelson and M. C. Cox, W. H. Freeman & Co., New York, 1119 pp (plus 17 pp glossary), ISBN 0-7167-4339-6 (2004). *Cell Biochemistry and Function* 23: 293-294, 2005.
16. **Carr AJ, Hopkins WG, and Gore CJ**. Effects of acute alkalosis and acidosis on performance: a meta-analysis. *Sports Med* 41: 801-814, 2011.
17. **Carr AJ, Slater GJ, Gore CJ, Dawson B, and Burke LM**. Effect of sodium bicarbonate on [HCO3-], pH, and gastrointestinal symptoms. *Int J Sport Nutr Exerc Metab* 21: 189-194, 2011.
18. **Carr AJ, Slater GJ, Gore CJ, Dawson B, and Burke LM**. Reliability and effect of sodium bicarbonate: buffering and 2000-m rowing performance. *Int J Sports Physiol Perform* 7: 152-160, 2012.
19. **Church DD, Hoffman JR, Varanoske AN, Wang R, Baker KM, La Monica MB, Beyer KS, Dodd SJ, Oliveira LP, Harris RC, Fukuda DH, and Stout JR**. Comparison of Two beta-Alanine Dosing Protocols on Muscle Carnosine Elevations. *Journal of the American College of Nutrition* 1-9, 2017.
20. **Cochran AJ, Percival ME, Thompson S, Gillen JB, MacInnis MJ, Potter MA, Tarnopolsky MA, and Gibala MJ**. beta-Alanine Supplementation Does Not Augment the Skeletal Muscle Adaptive Response to 6 Weeks of Sprint Interval Training. *Int J Sport Nutr Exerc Metab* 25: 541-549, 2015.

21. **Costill DL, Verstappen F, Kuipers H, Janssen E, and Fink W**. Acid-base balance during repeated bouts of exercise: influence of HCO3. *Int J Sports Med* 5: 228-231, 1984.
22. **de Oliveira LF, Saunders B, and Artioli GG**. Is Bypassing the Stomach a Means to Optimize Sodium Bicarbonate Supplementation? A Case Study With a Postbariatric Surgery Individual. *Int J Sport Nutr Exerc Metab* 28: 660-663, 2018.
23. **de Oliveira LF, Saunders B, Yamaguchi G, Swinton P, and Artioli GG**. Is Individualization of Sodium Bicarbonate Ingestion based on Time to Peak Necessary? *Med Sci Sports Exerc* 2020.
24. **Deb SK, Gough LA, Sparks SA, and McNaughton LR**. Determinants of curvature constant (W') of the power duration relationship under normoxia and hypoxia: the effect of pre-exercise alkalosis. *Eur J Appl Physiol* 117: 901-912, 2017.
25. **Debold EP, Fitts RH, Sundberg CW, and Nosek TM**. Muscle Fatigue from the Perspective of a Single Crossbridge. *Med Sci Sports Exerc* 48: 2270-2280, 2016.
26. **Decombaz J, Beaumont M, Vuichoud J, Bouisset F, and Stellingwerff T**. Effect of slow-release beta-alanine tablets on absorption kinetics and paresthesia. *Amino Acids* 43: 67-76, 2012.
27. **Derave W, Oezdemir MS, Harris RC, Pottier A, Reyngoudt H, Koppo K, Wise JA, and Achten E**. beta-alanine supplementation augments muscle carnosine content and attenuates fatigue during repeated isokinetic contraction bouts in trained sprinters. *J Appl Physiol* 103: 1736-1743, 2007.
28. **Dolan E, Saunders B, Harris RC, Bicudo J, Bishop DJ, Sale C, and Gualano B**. Comparative physiology investigations support a role for histidine-containing dipeptides in intracellular acid-base regulation of skeletal muscle. *Comp Biochem Physiol A Mol Integr Physiol* 234: 77-86, 2019.
29. **Dolan E, Swinton PA, Painelli VS, Stephens Hemingway B, Mazzolani B, Infante Smaira F, Saunders B, Artioli GG, and Gualano B**. A Systematic Risk Assessment and Meta-Analysis on the Use of Oral beta-Alanine Supplementation. *Adv Nutr* 2019.
30. **Donaldson SK, Hermansen L, and Bolles L**. Differential, direct effects of H+ on Ca2+ -activated force of skinned fibers from the soleus, cardiac and adductor magnus muscles of rabbits. *Pflugers Arch* 376: 55-65, 1978.
31. **Driller MW, Gregory JR, Williams AD, and Fell JW**. The Effects of Chronic Sodium Bicarbonate Ingestion and Interval Training in Highly Trained Rowers. *Int J Sport Nutr Exerc Metab* 23: 40-47, 2013.
32. **Ducker KJ, Dawson B, and Wallman KE**. Effect of Beta alanine and sodium bicarbonate supplementation on repeated-sprint performance. *J Strength Cond Res* 27: 3450-3460, 2013.
33. **Duncan MJ, Weldon A, and Price MJ**. The effect of sodium bicarbonate ingestion on back squat and bench press exercise to failure. *J Strength Cond Res* 28: 1358-1366, 2014.
34. **Durkalec-Michalski K, Zawieja EE, Podgorski T, Loniewski I, Zawieja BE, Warzybok M, and Jeszka J**. The effect of chronic progressive-dose sodium bicarbonate ingestion on CrossFit-like performance: A double-blind, randomized cross-over trial. *PloS one* 13: e0197480, 2018.
35. **Dutka TL, and Lamb GD**. Effect of carnosine on excitation-contraction coupling in mechanically-skinned rat skeletal muscle. *J Muscle Res Cell Motil* 25: 203-213, 2004.
36. **Edge J, Bishop D, and Goodman C**. Effects of chronic NaHCO3 ingestion during interval training on changes to muscle buffer capacity, metabolism, and short-term endurance performance. *J Appl Physiol (1985)* 101: 918-925, 2006.
37. **Fabiato A, and Fabiato F**. Effects of pH on the myofilaments and the sarcoplasmic reticulum of skinned cells from cardiace and skeletal muscles. *J Physiol* 276: 233-255, 1978.
38. **Fahey TD, Larsen JD, Brooks GA, Colvin W, Henderson S, and Lary D**. The effects of ingesting polylactate or glucose polymer drinks during prolonged exercise. *Int J Sport Nutr* 1: 249-256, 1991.
39. **Freis T, Hecksteden A, Such U, and Meyer T**. Effect of sodium bicarbonate on prolonged running performance: A randomized, double-blind, cross-over study. *PloS one* 12: e0182158, 2017.
40. **Froio de Araujo Dias G, da Eira Silva V, Painelli VS, Sale C, Giannini Artioli G, Gualano B, and Saunders B**. (In)Consistencies in Responses to Sodium Bicarbonate Supplementation: A Randomised, Repeated Measures, Counterbalanced and Double-Blind Study. *PloS one* 10: e0143086, 2015.

41. **Gough LA, Deb SK, Brown D, Sparks SA, and McNaughton LR**. The effects of sodium bicarbonate ingestion on cycling performance and acid base balance recovery in acute normobaric hypoxia. *J Sports Sci* 37: 1464-1471, 2019.
42. **Gough LA, Deb SK, Sparks A, and McNaughton LR**. The Reproducibility of 4-km Time Trial (TT) Performance Following Individualised Sodium Bicarbonate Supplementation: a Randomised Controlled Trial in Trained Cyclists. *Sports Med Open* 3: 34, 2017.
43. **Gough LA, Deb SK, Sparks AS, and McNaughton LR**. The Reproducibility of Blood Acid Base Responses in Male Collegiate Athletes Following Individualised Doses of Sodium Bicarbonate: A Randomised Controlled Crossover Study. *Sports Med* 47: 2117-2127, 2017.
44. **Gough LA, Deb SK, Sparks SA, and McNaughton LR**. Sodium bicarbonate improves 4 km time trial cycling performance when individualised to time to peak blood bicarbonate in trained male cyclists. *J Sports Sci* 1-8, 2017.
45. **Harris RC, Tallon MJ, Dunnett M, Boobis L, Coakley J, Kim HJ, Fallowfield JL, Hill CA, Sale C, and Wise JA**. The absorption of orally supplied beta-alanine and its effect on muscle carnosine synthesis in human vastus lateralis. *Amino Acids* 30: 279-289, 2006.
46. **Heibel AB, Perim PHL, Oliveira LF, McNaughton LR, and Saunders B**. Time to Optimize Supplementation: Modifying Factors Influencing the Individual Responses to Extracellular Buffering Agents. *Front Nutr* 5: 35, 2018.
47. **Heller MD, and Kern F, Jr.** Absorption of lactic acid from an isolated intestinal segment in the intact rat. *Proc Soc Exp Biol Med* 127: 1103-1106, 1968.
48. **Higgins MF, James RS, and Price MJ**. The effects of sodium bicarbonate (NaHCO3) ingestion on high intensity cycling capacity. *J Sport Sci* 31: 972-981, 2013.
49. **Hill CA, Harris RC, Kim HJ, Harris BD, Sale C, Boobis LH, Kim CK, and Wise JA**. Influence of beta-alanine supplementation on skeletal muscle carnosine concentrations and high intensity cycling capacity. *Amino Acids* 32: 225-233, 2007.
50. **Hilton NP, Leach NK, Sparks SA, Gough LA, Craig MM, Deb SK, and McNaughton LR**. A Novel Ingestion Strategy for Sodium Bicarbonate Supplementation in a Delayed-Release Form: a Randomised Crossover Study in Trained Males. *Sports Med Open* 5: 4, 2019.
51. **Hipkiss AR, and Brownson C**. A possible new role for the anti-ageing peptide carnosine. *Cell Mol Life Sci* 57: 747-753, 2000.
52. **Hoffman JR, Ratamess NA, Faigenbaum AD, Ross R, Kang J, Stout JR, and Wise JA**. Short-duration beta-alanine supplementation increases training volume and reduces subjective feelings of fatigue in college football players. *Nutr Res* 28: 31-35, 2008.
53. **Hultman E, and Sjoholm H**. Energy metabolism and contraction force of human skeletal muscle in situ during electrical stimulation. *J Physiol* 345: 525-532, 1983.
54. **Jacobs RA, Meinild AK, Nordsborg NB, and Lundby C**. Lactate oxidation in human skeletal muscle mitochondria. *American journal of physiology Endocrinology and metabolism* 304: E686-694, 2013.
55. **Jones RL, Barnett CT, Davidson J, Maritza B, Fraser WD, Harris R, and Sale C**. beta-alanine supplementation improves in-vivo fresh and fatigued skeletal muscle relaxation speed. *Eur J Appl Physiol* 117: 867-879, 2017.
56. **Jones RL, Stellingwerff T, Artioli GG, Saunders B, Cooper S, and Sale C**. Dose-Response of Sodium Bicarbonate Ingestion Highlights Individuality in Time Course of Blood Analyte Responses. *Int J Sport Nutr Exerc Metab* 26: 445-453, 2016.
57. **Jourkesh M, Ahmaidi S, Bita Mehdipoor K, Sadri I, and Ojagi A**. Effects of six weeks sodium bicarbonate supplementation and high-intensity interval training on endurance performance and body composition. *Ann Biol Res* 2: 403-413, 2011.
58. **Joyce S, Minahan C, Anderson M, and Osborne M**. Acute and chronic loading of sodium bicarbonate in highly trained swimmers. *Eur J Appl Physiol* 112: 461-469, 2012.
59. **Juel C**. Lactate-proton cotransport in skeletal muscle. *Physiol Rev* 77: 321-358, 1997.

60. **Katz A, Costill DL, King DS, Hargreaves M, and Fink WJ**. Maximal Exercise Tolerance after Induced Alkalosis. *Int J Sports Med* 5: 107-110, 1984.
61. **Kent-Braun JA, Fitts RH, and Christie A**. Skeletal muscle fatigue. *Compr Physiol* 2: 997-1044, 2012.
62. **Kowalchuk JM, Maltais SA, Yamaji K, and Hughson RL**. The effect of citrate loading on exercise performance, acid-base balance and metabolism. *Eur J Appl Physiol Occup Physiol* 58: 858-864, 1989.
63. **Krustrup P, Ermidis G, and Mohr M**. Sodium bicarbonate intake improves high-intensity intermittent exercise performance in trained young men. *J Int Soc Sports Nutr* 12: 2015.
64. **Lancha Junior AH, Painelli VS, Saunders B, and Artioli GG**. Nutritional Strategies to Modulate Intracellular and Extracellular Buffering Capacity During High-Intensity Exercise. *Sports Med* 45 Suppl 1: S71-81, 2015.
65. **Linderman JK, and Gosselink KL**. The effects of sodium bicarbonate ingestion on exercise performance. *Sports Med* 18: 75-80, 1994.
66. **Liu Q, Sikand P, Ma C, Tang Z, Han L, Li Z, Sun S, LaMotte RH, and Dong X**. Mechanisms of itch evoked by beta-alanine. *J Neurosci* 32: 14532-14537, 2012.
67. **Matson LG, and Tran ZV**. Effects of sodium bicarbonate ingestion on anaerobic performance: a meta-analytic review. *Int J Sport Nutr* 3: 2-28, 1993.
68. **Maughan RJ, Burke LM, Dvorak J, Larson-Meyer DE, Peeling P, Phillips SM, Rawson ES, Walsh NP, Garthe I, Geyer H, Meeusen R, van Loon LJC, Shirreffs SM, Spriet LL, Stuart M, Vernec A, Currell K, Ali VM, Budgett RG, Ljungqvist A, Mountjoy M, Pitsiladis YP, Soligard T, Erdener U, and Engebretsen L**. IOC consensus statement: dietary supplements and the high-performance athlete. *Br J Sports Med* 52: 439-455, 2018.
69. **Mazzeo RS, Brooks GA, Schoeller DA, and Budinger TF**. Disposal of blood [1-13C]lactate in humans during rest and exercise. *J Appl Physiol (1985)* 60: 232-241, 1986.
70. **McNaughton L, and Cedaro R**. Sodium citrate ingestion and its effects on maximal anaerobic exercise of different durations. *Eur J Appl Physiol Occup Physiol* 64: 36-41, 1992.
71. **McNaughton L, and Thompson D**. Acute versus chronic sodium bicarbonate ingestion and anaerobic work and power output. *J Sports Med Phys Fitness* 41: 456-462, 2001.
72. **McNaughton LR**. Bicarbonate ingestion: Effects of dosage on 60 s cycle ergometry. *J Sport Sci* 10: 415-423, 1992.
73. **McNaughton LR**. Sodium bicarbonate ingestion and its effects on anaerobic exercise of various durations. *J Sports Sci* 10: 425-435, 1992.
74. **McNaughton LR**. Sodium citrate and anaerobic performance: implications of dosage. *Eur J Appl Physiol Occup Physiol* 61: 392-397, 1990.
75. **Miller P, Robinson AL, Sparks SA, Bridge CA, Bentley DJ, and McNaughton LR**. The Effects of Novel Ingestion of Sodium Bicarbonate on Repeated Sprint Ability. *J Strength Cond Res* 30: 561-568, 2016.
76. **Morris D**. Effects of oral lactate consumption on metabolism and exercise performance. *Curr Sports Med Rep* 11: 185-188, 2012.
77. **Morris D, Beloni R, and Wofford H**. Metabolic and Exercise Performance Responses to Two Different Oral Doses of Calcium Lactate. *Med Sci Sport Exer* 48: 250-250, 2016.
78. **Morris DM, Shafer RS, Fairbrother KR, and Woodall MW**. Effects of lactate consumption on blood bicarbonate levels and performance during high-intensity exercise. *Int J Sport Nutr Exerc Metab* 21: 311-317, 2011.
79. **Mueller SM, Gehrig SM, Frese S, Wagner CA, Boutellier U, and Toigo M**. Multiday acute sodium bicarbonate intake improves endurance capacity and reduces acidosis in men. *J Int Soc Sports Nutr* 10: 16, 2013.
80. **Mundel T**. Sodium bicarbonate ingestion improves repeated high-intensity cycling performance in the heat. *Temperature* 5: 343-347, 2018.

81. **Northgraves MJ, Peart DJ, Jordan CA, and Vince RV**. Effect of lactate supplementation and sodium bicarbonate on 40-km cycling time trial performance. *J Strength Cond Res* 28: 273-280, 2014.
82. **Oliveira LF, de Salles Painelli V, Nemezio K, Goncalves LS, Yamaguchi G, Saunders B, Gualano B, and Artioli GG**. Chronic lactate supplementation does not improve blood buffering capacity and repeated high-intensity exercise. *Scand J Med Sci Sports* 27: 1231-1239, 2017.
83. **Oopik V, Saaremets I, Medijainen L, Karelson K, Janson T, and Timpmann S**. Effects of sodium citrate ingestion before exercise on endurance performance in well trained college runners. *Br J Sports Med* 37: 485-489, 2003.
84. **Oopik V, Saaremets I, Timpmann S, Medijainen L, and Karelson K**. Effects of acute ingestion of sodium citrate on metabolism and 5-km running performance: a field study. *Canadian journal of applied physiology = Revue canadienne de physiologie appliquee* 29: 691-703, 2004.
85. **Painelli VS, da Silva RP, de Oliveira OM, Jr., de Oliveira LF, Benatti FB, Rabelo T, Guilherme JP, Lancha AH, Jr., and Artioli GG**. The effects of two different doses of calcium lactate on blood pH, bicarbonate, and repeated high-intensity exercise performance. *Int J Sport Nutr Exerc Metab* 24: 286-295, 2014.
86. **Painelli VS, and Lancha Junior AH**. Thirty years of investigation on the ergogenic effects of sodium citrate: is it time for a fresh start? *Br J Sports Med* 2016.
87. **Painelli VS, Saunders B, Sale C, Harris RC, Solis MY, Roschel H, Gualano B, Artioli GG, and Lancha AH, Jr.** Influence of training status on high-intensity intermittent performance in response to beta-alanine supplementation. *Amino Acids* 46: 1207-1215, 2014.
88. **Pan JW, Hamm JR, Hetherington HP, Rothman DL, and Shulman RG**. Correlation of lactate and pH in human skeletal muscle after exercise by 1H NMR. *Magnetic resonance in medicine* 20: 57-65, 1991.
89. **Parry-Billings M, and MacLaren DP**. The effect of sodium bicarbonate and sodium citrate ingestion on anaerobic power during intermittent exercise. *Eur J Appl Physiol Occup Physiol* 55: 524-529, 1986.
90. **Peart DJ, Siegler JC, and Vince RV**. Practical recommendations for coaches and athletes: a meta-analysis of sodium bicarbonate use for athletic performance. *J Strength Cond Res* 26: 1975-1983, 2012.
91. **Peeling P, Binnie MJ, Goods PSR, Sim M, and Burke LM**. Evidence-Based Supplements for the Enhancement of Athletic Performance. *Int J Sport Nutr Exerc Metab* 28: 178-187, 2018.
92. **Price MJ, and Singh M**. Time course of blood bicarbonate and pH three hours after sodium bicarbonate ingestion. *Int J Sports Physiol Perform* 3: 240-242, 2008.
93. **Rampinini E, Sassi A, Morelli A, Mazzoni S, Fanchini M, and Coutts AJ**. Repeated-sprint ability in professional and amateur soccer players. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme* 34: 1048-1054, 2009.
94. **Renfree A**. The time course for changes in plasma [h+] after sodium bicarbonate ingestion. *Int J Sports Physiol Perform* 2: 323-326, 2007.
95. **Requena B, Zabala M, Padial P, and Feriche B**. Sodium bicarbonate and sodium citrate: ergogenic aids? *J Strength Cond Res* 19: 213-224, 2005.
96. **Robergs R, Hutchinson K, Hendee S, Madden S, and Siegler J**. Influence of pre-exercise acidosis and alkalosis on the kinetics of acid-base recovery following intense exercise. *Int J Sport Nutr Exerc Metab* 15: 59-74, 2005.
97. **Sahlin K, Harris RC, and Hultman E**. Creatine kinase equilibrium and lactate content compared with muscle pH in tissue samples obtained after isometric exercise. *The Biochemical journal* 152: 173-180, 1975.
98. **Sahlin K, Harris RC, Nylind B, and Hultman E**. Lactate Content and Ph in Muscle Samples Obtained after Dynamic Exercise. *Pflug Arch Eur J Phy* 367: 143-149, 1976.
99. **Sale C, Artioli GG, Gualano B, Saunders B, Hobson RM, and Harris RC**. Carnosine: from exercise performance to health. *Amino Acids* 44: 1477-1491, 2013.

100. **Sale C, Hill CA, Ponte J, and Harris RC**. beta-alanine supplementation improves isometric endurance of the knee extensor muscles. *J Int Soc Sports Nutr* 9: 26, 2012.
101. **Sale C, Saunders B, Hudson S, Wise JA, Harris RC, and Sunderland CD**. Effect of beta-Alanine Plus Sodium Bicarbonate on High-Intensity Cycling Capacity. *Med Sci Sport Exer* 43: 1972-1978, 2011.
102. **Saunders B, Elliott-Sale K, Artioli GG, Swinton PA, Dolan E, Roschel H, Sale C, and Gualano B**. Beta-alanine supplementation to improve exercise capacity and performance: a systematic review and meta-analysis. *Br J Sports Med* 51: 658-669, 2017.
103. **Saunders B, Franchi M, Oliveira LF, Silva VE, Silva RP, Painelli VS, Costa LAR, Sale C, Harris RC, Roschel H, Artioli GG, and Gualano B**. 24-Wk β-Alanine Ingestion Does Not Affect Muscle Taurine Or Clinical Blood Parameters. *Eur J Nutr* 59: 57-65, 2020.
104. **Saunders B, Painelli VS, LF DEO, V DAES, RP DAS, Riani L, Franchi M, Goncalves LS, Harris RC, Roschel H, Artioli GG, Sale C, and Gualano B**. Twenty-four Weeks of beta-Alanine Supplementation on Carnosine Content, Related Genes, and Exercise. *Med Sci Sports Exerc* 49: 896-906, 2017.
105. **Saunders B, Sale C, Harris RC, and Sunderland C**. Effect of beta-alanine supplementation on repeated sprint performance during the Loughborough Intermittent Shuttle Test. *Amino Acids* 43: 39-47, 2012.
106. **Saunders B, Sale C, Harris RC, and Sunderland C**. Effect of sodium bicarbonate and Beta-alanine on repeated sprints during intermittent exercise performed in hypoxia. *Int J Sport Nutr Exerc Metab* 24: 196-205, 2014.
107. **Saunders B, Sale C, Harris RC, and Sunderland C**. Sodium bicarbonate and high-intensity-cycling capacity: variability in responses. *Int J Sports Physiol Perform* 9: 627-632, 2014.
108. **Saunders B, Sunderland C, Harris RC, and Sale C**. beta-alanine supplementation improves YoYo intermittent recovery test performance. *J Int Soc Sports Nutr* 9: 39, 2012.
109. **Schabort EJ, Wilson G, and Noakes TD**. Dose-related elevations in venous pH with citrate ingestion do not alter 40-km cycling time-trial performance. *Eur J Appl Physiol* 83: 320-327, 2000.
110. **Shave R, Whyte G, Siemann A, and Doggart L**. The effects of sodium citrate ingestion on 3,000-meter time-trial performance. *J Strength Cond Res* 15: 230-234, 2001.
111. **Siegler JC, Marshall PWM, Bray J, and Towlson C**. Sodium Bicarbonate Supplementation and Ingestion Timing: Does It Matter? *J Strength Cond Res* 26: 1953-1958, 2012.
112. **Siegler JC, Midgley AW, Polman RC, and Lever R**. Effects of various sodium bicarbonate loading protocols on the time-dependent extracellular buffering profile. *J Strength Cond Res* 24: 2551-2557, 2010.
113. **Smith AE, Moon JR, Kendall KL, Graef JL, Lockwood CM, Walter AA, Beck TW, Cramer JT, and Stout JR**. The effects of beta-alanine supplementation and high-intensity interval training on neuromuscular fatigue and muscle function. *Eur J Appl Physiol* 105: 357-363, 2009.
114. **Smith AE, Walter AA, Graef JL, Kendall KL, Moon JR, Lockwood CM, Fukuda DH, Beck TW, Cramer JT, and Stout JR**. Effects of beta-alanine supplementation and high-intensity interval training on endurance performance and body composition in men; a double-blind trial. *J Int Soc Sports Nutr* 6: 5, 2009.
115. **Spencer M, Bishop D, Dawson B, and Goodman C**. Physiological and metabolic responses of repeated-sprint activities:specific to field-based team sports. *Sports Med* 35: 1025-1044, 2005.
116. **Stellingwerff T, Anwander H, Egger A, Buehler T, Kreis R, Decombaz J, and Boesch C**. Effect of two beta-alanine dosing protocols on muscle carnosine synthesis and washout. *Amino Acids* 42: 2461-2472, 2012.
117. **Stephens TJ, McKenna MJ, Canny BJ, Snow RJ, and McConell GK**. Effect of sodium bicarbonate on muscle metabolism during intense endurance cycling. *Med Sci Sports Exerc* 34: 614-621, 2002.
118. **Sundberg CW, and Fitts RH**. Bioenergetic basis of skeletal muscle fatigue. *Curr Opin Physiol* 10: 118-127, 2019.

119. **Sundberg CW, Hunter SK, Trappe SW, Smith CS, and Fitts RH**. Effects of elevated H(+) and Pi on the contractile mechanics of skeletal muscle fibres from young and old men: implications for muscle fatigue in humans. *J Physiol* 596: 3993-4015, 2018.
120. **Sutton JR, Jones NL, and Toews CJ**. Effect of PH on muscle glycolysis during exercise. *Clin Sci (Lond)* 61: 331-338, 1981.
121. **Sweeney KM, Wright GA, Glenn Brice A, and Doberstein ST**. The effect of beta-alanine supplementation on power performance during repeated sprint activity. *J Strength Cond Res* 24: 79-87, 2010.
122. **Tesch PA, Colliander EB, and Kaiser P**. Muscle metabolism during intense, heavy-resistance exercise. *Eur J Appl Physiol Occup Physiol* 55: 362-366, 1986.
123. **Tobias G, Benatti FB, Painelli VS, Roschel H, Gualano B, Sale C, Harris RC, Lancha AH, Jr., and Artioli GG**. Additive effects of beta-alanine and sodium bicarbonate on upper-body intermittent performance. *Amino Acids* 45: 309-317, 2013.
124. **Urwin CS, Dwyer DB, and Carr AJ**. Induced Alkalosis and Gastrointestinal Symptoms After Sodium Citrate Ingestion: a Dose-Response Investigation. *Int J Sport Nutr Exerc Metab* 26: 542-548, 2016.
125. **Van Montfoort MC, Van Dieren L, Hopkins WG, and Shearman JP**. Effects of ingestion of bicarbonate, citrate, lactate, and chloride on sprint running. *Med Sci Sports Exerc* 36: 1239-1243, 2004.
126. **Walter AA, Smith AE, Kendall KL, Stout JR, and Cramer JT**. Six weeks of high-intensity interval training with and without beta-alanine supplementation for improving cardiovascular fitness in women. *J Strength Cond Res* 24: 1199-1207, 2010.
127. **Wang J, Qiu J, Yi L, Hou Z, Benardot D, and Cao W**. Effect of sodium bicarbonate ingestion during 6 weeks of HIIT on anaerobic performance of college students. *J Int Soc Sports Nutr* 16: 18, 2019.

Table 1. Dissociation constant (Ka) and its negative log (pKa) of a few organic weak acids.

Acid	Ka	pKa
Pyruvic Acid	3.98×10^{-3}	2.4
Citric Acid	7.94×10^{-4}	3.1
Formic Acid	1.78×10^{-4}	3.75
Imidazole	1.26×10^{-7}	6.9

Table 2. The pKa of ionisable groups of the amino acids.

Amino Acid	pKa of COOH	pKa of NH_2	pKa of side-chain
Alanine	2.34	9.69	–
Arginine	2.17	9.04	12.48
Asparagine	2.02	8.80	–
Aspartic acid	1.88	9.60	3.65
Cysteine	1.96	10.28	8.18
Glutamic acid	2.19	9.67	4.25
Glutamine	2.17	9.13	–
Glycine	2.34	9.60	–
Histidine	1.82	9.17	6.00
Hydroxyproline	1.82	9.65	–
Isoleucine	2.36	9.60	–
Leucine	2.36	9.60	–
Lysine	2.18	8.95	10.53
Methionine	2.28	9.21	–
Phenylalanine	1.83	9.13	–
Proline	1.99	10.60	–
Serine	2.21	9.15	–
Threonine	2.09	9.10	–
Tryptophan	2.83	9.39	–
Tyrosine	2.20	9.11	10.07
Valine	2.32	9.62	–

Source: (15)

Figure 1.

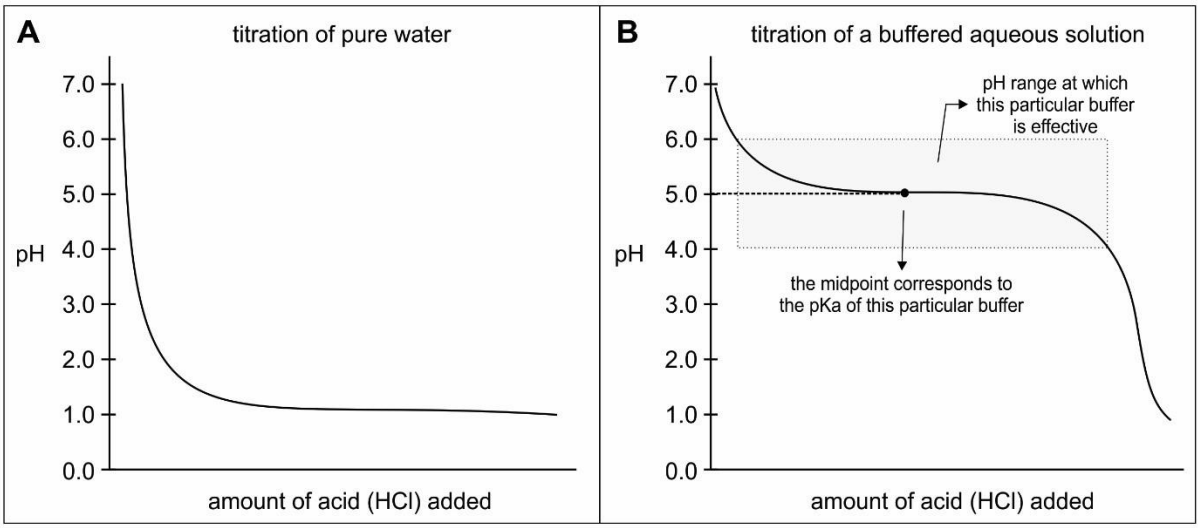

A
titration of pure water
7.0
6.0
5.0
pH 4.0
3.0
2.0
1.0
0.0
amount of acid (HCl) added
B
titration of a buffered aqueous solution
pH range at which this particular buffer is effective
the midpoint corresponds to the pKa of this particular buffer
7.0
6.0
5.0
pH 4.0
3.0
2.0
1.0
0.0
amount of acid (HCl) added

Figure 2.

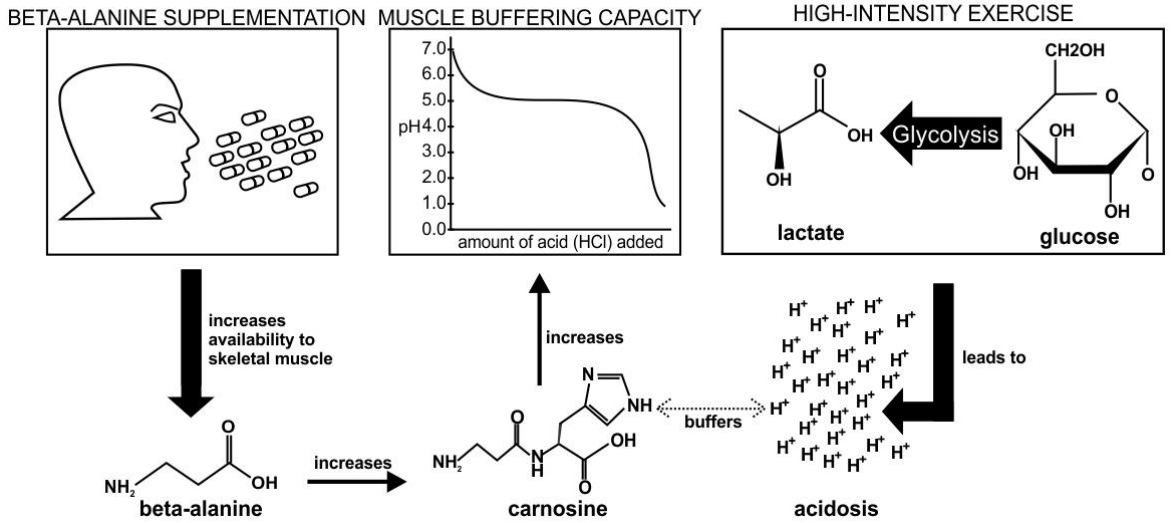
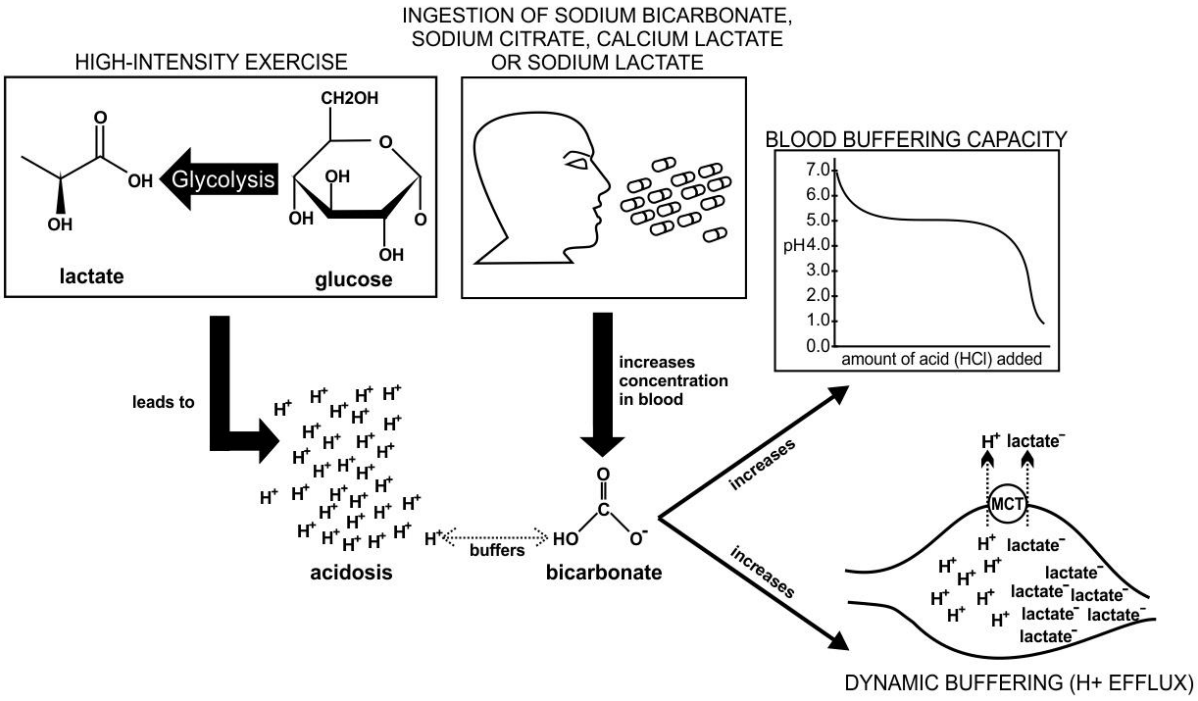

BETA-ALANINE SUPPLEMENTATION
MUSCLE BUFFERING CAPACITY
HIGH-INTENSITY EXERCISE
7.0
6.0
5.0
pH4.0
3.0
2.0
1.0
0.0
amount of acid (HCl) added
Glycolysis
CH2OH
lactate
glucose
increases availability to skeletal muscle
increases
leads to
buffers
increases
beta-alanine
carnosine
acidosis

Figure 3.


INGESTION OF SODIUM BICARBONATE,
SODIUM CITRATE, CALCIUM LACTATE
OR SODIUM LACTATE
HIGH-INTENSITY EXERCISE
Glycolysis
lactate
glucose
BLOOD BUFFERING CAPACITY
amount of acid (HCl) added
leads to
increases
concentration
in blood
acidosis
buffers
bicarbonate
increases
increases
MCT
DYNAMIC BUFFERING (H+ EFFLUX)