Effects of Dietary Supplements on Adaptations to Endurance Training

Effects of Dietary Supplements on Adaptations to Endurance Training

Short title/running head: Supplements and Training Adaptations

(1, 2) Jeffrey A. Rothschild*

(3, 4) David J. Bishop

Affiliations

(1) Sports Performance Research Institute New Zealand (SPRINZ), Auckland University of Technology
Auckland, New Zealand
Email: rd@trifitla.com
Orcid: 0000-0003-0014-5878
*Corresponding author

(2) TriFit Performance Center
Santa Monica, CA, United States

(3) Institute for Health and Sport, Victoria University
Melbourne, VIC, Australia
Email: David.Bishop@vu.edu.au
Orcid: 0000-0002-6956-9188

(4) School of Medical and Health Sciences, Edith Cowan University
Joondalup, Western Australia, Australia

Abstract

Endurance training leads to a variety of adaptations at the cellular and systemic levels that serve to minimise disruptions in whole-body homeostasis caused by exercise. These adaptations are differentially affected by training volume, training intensity, and training status, as well as by nutritional choices that can enhance or impair the response to training. A variety of supplements have been studied in the context of acute performance enhancement, but the effects of continued supplementation concurrent to endurance training programs are less well characterised. For example, supplements such as sodium bicarbonate and beta-alanine can improve endurance performance and possibly training adaptations during endurance training by affecting buffering capacity and/or allowing an increased training intensity, while antioxidants such as vitamin C and vitamin E may impair training adaptations by blunting cellular signaling but appear to have little effect on

performance outcomes. Additionally, limited data suggest the potential for dietary nitrate (in the form of beetroot juice), creatine, and possibly caffeine, to further enhance endurance training adaptation. Therefore, the objective of this review is to examine the impact of dietary supplements on metabolic and physiological adaptations to endurance training.

Abstract word count: 185
Word count: 6,498
Number of tables: 5
Number of figures: 4

Key Points

- Many supplements have been studied in the context of acute performance enhancement, but the effects of continued supplementation concurrent to endurance training programs are less well characterised.
- Supplements including sodium bicarbonate, beta-alanine, dietary nitrates, antioxidants, caffeine, and creatine have the potential to modify the adaptive response to endurance training (either positively or negatively) by affecting acid-base balance, redox status, oxidant signaling, or cumulative training load, thereby affecting the cellular signaling responses to training.

1. Introduction

Endurance training (repeated sessions of continuous or intermittent exercise performed with the goal of improving endurance performance) leads to metabolic and morphological adaptations at the cellular and systemic levels, which allow submaximal-intensity exercise to be performed with a smaller homeostatic disturbance [1]. These adaptations include increases in maximal oxygen uptake (VO_{2max}), mitochondrial enzyme activity, and mitochondrial protein content, which result in a shift towards greater reliance on fat for fuel, reduced glycolytic flux, decreased lactate accumulation at a given work rate, and tighter control of acid–base balance [1-3].

Training-induced adaptations are the consequence of repeated stimuli from individual exercise sessions [3], and the accumulation over time of transient, exercise-induced changes in gene expression [4]. Manipulation of training intensity and duration are the primary variables affecting the exercise response [5]. However, dietary intake can also impact adaptations to training by increasing the exercise stimulus and/or enhancing or blunting cellular responses to exercise-induced perturbations (Fig. 1) [6].

Elite athletes use dietary supplements more than non-elite athletes, with a similar prevalence between men and women [7]. Although the motivations for using these supplements are often not with the goal of improving adaptations to training, the use of dietary supplements represents an under-researched and under-appreciated approach for impacting the adaptive response to endurance training.

The performance effects of supplements commonly used by endurance athletes, including sodium bicarbonate, β-alanine, and dietary nitrates, has been reviewed [8-13]. However, these supplements are typically considered only in the context of acute performance changes and less is known about how they influence adaptations to training. These supplements have the potential to modify the adaptive response to endurance training (either positively or negatively) by affecting acid-base balance, redox status, reactive oxygen species (ROS) signaling, or cumulative training load, thereby affecting the cellular signaling responses to training (Fig. 2). Some discussion of the effects of supplements on training adaptations has previously been published [14-16], but these were focused on a narrow subset of

supplements and did not include creatine or caffeine, or research published over the past five years. Thus, an updated overview of the current literature is warranted. The objective of this review is to examine the impact of common dietary supplements on the metabolic and physiological adaptations to endurance training.

2. Buffering Agents

Supplements that act on buffering and pH regulation may affect the training response by allowing an athlete to train harder (increasing the exercise stimulus), and/or impacting important signaling molecules, such as the 5' AMP-activated protein kinase (AMPK), p38 mitogen-activated protein kinase (MAPK), and the Ca^{2+}/calmodulin-dependent kinase (CaMK) pathways, which are affected by pH [17-19]. For example, an acidic pH decreased the protein content of phosphorylated AMPK in differentiated L6 myotubes [19], cultured fibroblasts [20], and rat cardiomyocytes [21], while an alkaline pH increased phosphorylated AMPK protein content in rat cardiomyocytes [21]. In humans, inducing acidosis with ammonium chloride before a session of interval exercise blunted the post-exercise increases in peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), citrate synthase (CS), cytochrome C (CYT-C), and *GLUT4* mRNA compared with a placebo [22] (Fig. 3). Blood lactate concentrations are also decreased in acidosis, likely due to the attenuation of glycolytic activity [23]. This may negatively impact training adaptations as lactate signaling can influence mitochondrial biogenesis [24] and the chronic adaptive response to training [25]. An increase in blood pH can increase the rate of muscle glycogen breakdown along with increasing blood lactate levels and H^+ efflux out of contracting muscles [26, 27]. Increasing blood pH via ingestion of sodium bicarbonate prior to a session of high-intensity exercise

117 increased the expression of *PGC-1α* mRNA to a greater degree than a placebo [27]. Although
118 acute responses to training do not always correspond with long-term adaptations [28], there
119 is evidence to suggest that supplements that alter pH may affect adaptations to training.
120
121 *2.1 Sodium Bicarbonate*
122 Sodium bicarbonate is typically consumed in a dose of 0.2 to 0.4 grams per kg of bodyweight,
123 divided across one to three servings [16], although serial loading protocols over several days
124 have also been used [29]. This dose should be sufficient to raise bicarbonate concentrations
125 in the blood by 5 to 6 mmol/L and allow small changes in blood pH during sub-maximal
126 exercise, although large interindividual variability in the response to supplementation has
127 been reported [30-32]. Ingestion of sodium bicarbonate before each cycling interval training
128 session (24 sessions over eight weeks) in recreationally-active women resulted in greater
129 improvements in the lactate threshold (26 vs. 15%, d = 0.5) and time to fatigue (164 vs 123%,
130 d = 1.9) compared with a placebo, even though training volume and intensity was matched
131 between groups (Table 1) [33]. Six weeks of high-intensity interval training (HIIT) (18
132 sessions) by recreationally-active men consuming sodium bicarbonate or a placebo prior to
133 each training session led to greater improvement in relative peak power (20.8 vs. 10.3%, d
134 = 2.1) but no differences in relative mean power on a Wingate test [34], and similar
135 improvements in time to fatigue, maximum power, and lactate threshold power, though only
136 the bicarbonate group had significant increases in CS activity (22.3 vs. 12.6%) [35]. However,
137 four weeks of sodium bicarbonate supplementation in highly-trained male rowers did not
138 provide significant performance benefits compared with a placebo [36]. While favourable
139 trends were observed for 2,000-m power, peak power, and power at the lactate threshold, it

is possible that performing only 8 sessions over the 4-week study period and/or the small sample size (n=6 per group) was not sufficient to detect significant changes.

Rats performing HIIT on a treadmill five times per week for five weeks had a 52% longer time to exhaustion (*d* = 11.1), and greater improvements in ADP-stimulated mitochondrial respiration (*d* = 1.8), when consuming sodium bicarbonate before exercise, compared with rats that ingested a placebo prior to exercise [37, 38]. These groups were also matched for total work performed during each training session, further supporting the potential for bicarbonate to improve adaptations to training. Changes in the activity of CS and phosphofructokinase, and sodium bicarbonate cotransporter protein content, were similar to the placebo group [37, 38], although levels of monocarboxylate transporter 4 increased to a greater degree after training with bicarbonate supplementation [38].

Overall, sodium bicarbonate is unlikely to have an effect on VO_{2max} (which is largely affected by central adaptations [39]), but may affect peripheral adaptations that are influenced by pH such as the lactate threshold, CS activity, and mitochondrial respiration, particularly in untrained participants (Fig. 3). Contrasting results may be due to differences in fitness level, number and intensity of training sessions performed, sex differences, genetics, and sample size. Two studies that showed no differences between groups prescribed HIIT at a percentage of peak power [35, 36], while a study that set training intensity as a percentage of the lactate threshold resulted in improved performance [33].

Future research should elucidate differences in mitochondrial enzyme content and respiration as a result of sodium bicarbonate ingestion prior to training sessions. Exercise stimuli should be sufficient to alter lactate levels and/or pH compared with a placebo, and should compare both work-matched and time-based (e.g., 4-min intervals at maximal effort) intervals to examine the effects of differences in pH versus differences in total work during training sessions.

2.2 Beta-alanine

Beta-alanine is an increasingly popular supplement for athletes due to its ability to delay fatigue during high-intensity exercise. It does this by increasing muscle carnosine content in a dose-dependent manner [40], and improvements in exercise performance have been shown with doses ranging from 3.2 to 6.4 g/day for 4 to 24 weeks [9]. β-alanine has the potential to enhance training adaptations by increasing the ability to sustain exercise at a higher intensity [41], and allowing athletes to better tolerate greater training volumes with decreased subjective feelings of fatigue [42]. As β-alanine is considered primarily effective within 1- to 10-minute time frames [9], endurance athletes who undertake interval training sessions within that duration may benefit from an improved adaptive response to training by accumulating a greater workload during each session. This may be due to a number of inter-related factors including improved pH buffering [43], which can allow a greater reliance on aerobic metabolism and thus reduced accumulation of glycolytic metabolites for the same exercise intensity [44], decreased levels of blood lactate during the recovery from supra-maximal exercise [45], a reduction in oxidative stress due to the antioxidant effects of carnosine that could allow improved recovery between demanding workouts [46-48], an

185 increased threshold for neuromuscular fatigue [41], and/or reduced feelings of fatigue
186 during periods of heavy training [42, 44]. It has also been suggested that increases in calcium
187 sensitivity [49], or in calcium re-uptake [50], may also play a role in the ergogenic effects of
188 β-alanine by helping to slow the decline in muscle performance during fatiguing exercise.
189 From a cell-signaling perspective, β-alanine supplementation may impact mitochondrial
190 biogenesis via increased calcium re-uptake [50] and its downstream effects on AMPK, CaMK,
191 and extracellular-signal-regulated kinases (ERK) 1 and 2 [51], increased expression of
192 peroxisome proliferator-activated receptor (PPAR)β/δ [52], and/or greater lactate signaling
193 [24, 53] (Fig. 2).
194
195 Most studies have investigated the effects of β-alanine on exercise performance, with
196 relatively few studies considering the effects of supplementation on adaptations to training
197 (Table 1). Of the studies that have measured changes in VO_{2peak} after endurance training,
198 none have reported greater improvements from supplementation compared with the
199 placebo groups [53-57]. This finding is similar to sodium bicarbonate and would be expected
200 as buffering agents are more likely to exert their effects in the skeletal muscle rather than
201 through central mechanisms. However, similar increases in cytochrome-c oxidase and β-
202 hydroxyacyl-CoA dehydrogenase (β-HAD) maximal activities were found in active but
203 untrained men taking β-alanine or a placebo during six weeks of Sprint Interval Training
204 (SIT) (three sessions per week) [55], suggesting differences in peripheral adaptations may
205 not be seen when total work performed is the same. This is in contrast to some findings for
206 sodium bicarbonate [33, 34].
207

Performance improvements with β-alanine supplementation, compared with a placebo, have been reported for 10-km time-trial running performance (~54 min) following three weeks of run training [58], and cycling time-to-exhaustion at 120% of peak power (~3.5 min) following a five-week SIT program [53] (Table 1). There was also a trend for greater improvement in cycling time-to-exhaustion at 110% of peak power (~23 min) after six weeks of HIIT [57]. In contrast, four to six weeks of interval training in recreationally-active participants taking β-alanine or a placebo resulted in similar improvements for 250-kJ (~20 min) time-trial performance [55], average power during a 4-min time-trial [59], power at the ventilatory threshold [54], and critical power during a 3-minute all-out cycling test [56]. Considering its established effects on high-intensity exercise performance [9], it is challenging to distinguish the effects of β-alanine on performance from its effects on adaptations to training. However, as shown in Figure 4, there appear to be both independent and additive benefits of SIT and β-alanine supplementation.

One of the proposed mechanisms for β-alanine to improve training adaptations is an increased training intensity. This was observed in one study that showed improvements [53], while a trend for increased training intensity was seen in another that also showed favorable improvements [57]. Furthermore, there were increased blood lactate levels during sprint intervals with supplementation, compared with a placebo [53, 60]. Although training intensities were not reported in two other studies that showed improvements, they used interval-training protocols that elicited maximal, rather than pre-determined, effort levels [56, 58]. No differences in training intensity were seen in studies that showed no additional improvements from β-alanine either with maximal (30-s) sprint training [55] or sprints at

pre-determined work intensities [54, 59, 61]. This suggests greater training adaptations with β-alanine supplementation are less likely to be observed if training intensities are intentionally clamped or the chosen interval prescriptions are outside of the 1 to 10 minute range of exercise where β-alanine exerts its most prominent influence [62]. With typical dosing regimens of 3.2 to 6.4 g/d, at least two weeks of supplementation is needed to elevate muscle carnosine concentrations [40, 63], before potentially exerting beneficial effects on training intensity. Therefore, muscle carnosine loading may be beneficial prior to undertaking an exercise training study.

2.3 Summary

The use of sodium bicarbonate (which causes an acute change in blood buffering capacity) or β-alanine (which causes a chronic change in muscle buffering capacity) show potential for allowing greater adaptations to training, though the data are mixed. Contrasting results may be due to differences in training status, training intensity, or the use of interval prescriptions that clamp exercise intensities and/or may fall outside of the optimal duration for the supplement to be effective (e.g. <60 s). Furthermore, responses to sodium bicarbonate appear subject to both intra-[31] and inter-[64] individual variability, at least in untrained participants. Although the performance effects of co-ingesting sodium bicarbonate and β-alanine are unclear [65], several studies have investigated the effects of combined supplementation on training adaptations [66-68]. While a 4-wk loading period of β-alanine supplementation is typically used when studying co-ingestion, in all but one study [61] participant training sessions were not monitored. As discussed, differences in training

intensity appear necessary to see beneficial training adaptations with β-alanine supplementation.

Research using doses that have been shown to increase blood pH or muscle carnosine content should investigate the longer-term effects of sodium bicarbonate and β-alanine supplementation on training capacity to determine if athletes can increase their training volume, which could allow greater training adaptations and, in turn, better performance, as well as the effects of training status on training adaptations. Particularly for β-alanine, interval prescriptions should avoid pre-determined workloads (e.g. 4 min at 90% of peak power), in favor of distance or time-based intervals (e.g. 1-km, or 4-min maximal efforts). If set workloads are required, using a percentage of lactate threshold may be preferable to a percentage of VO_{2peak}. In addition to work completed during each session, measurement of blood lactate concentrations may be useful in determining if changes in lactate levels, compared with a placebo, can be predictive of an augmented training response (Table 2).

3. Dietary Nitrate

Dietary nitrate (NO_3^-), commonly supplemented and studied in the form of beetroot juice, has the potential to augment adaptations to endurance training due to its ability to increase plasma levels of nitrite (NO_2^-) and nitric oxide (NO) [69]. It can increase training intensity [70] (and thus total amount of work completed in a workout) by enhancing mitochondrial efficiency [71], reducing the oxygen cost of muscle contraction [72], and increasing contractile force in fast-twitch muscles [73]. Increases in mitochondrial biogenesis (via NO stimulation of guanylate cyclase leading to activation of PGC-1α) [74], and a shift in muscle

fibre type towards a more oxidative phenotype when combined with SIT (via nitric oxide's role in calcineurin–NFAT [nuclear factor of activated T-cells] signaling) have also been reported [75-77], which are possibly related to increases in mitochondrial hydrogen peroxide [78]. However, by reducing the oxygen cost of muscle contraction, thereby reducing the metabolic stress inside the muscle, it is also possible that nitrate supplementation may impair training adaptations via decreased activation of cell-signaling pathways (e.g. AMPK, CaMK, and PGC-1α) [79].

The majority of studies showing beneficial effects of supplementation on endurance performance have used doses of 6 to 8 mmol NO_3^- taken as a single dose 2 to 3 hours prior to exercise or with a loading period of 5 to 8 days [10], although higher doses (e.g. 8 to 12 mmol) may be required for elite athletes [80]. Plasma levels of NO_2^-, used as a marker of NO availability [81], are increased in a dose-dependent manner but benefits may plateau between 8 and 16 mmol NO_3^- [82]. No effects of beetroot juice were observed after six weeks of cycling HIIT when ingesting ~5 mmol NO_3^- per day [83], while training studies using 8 to 12.8 mmol NO_3^- per day have shown benefits [75, 84-86].

Seven studies have supplemented dietary nitrate while undergoing supervised endurance training for at least three weeks [75, 77, 83-87] (Table 3). Four weeks of SIT combined with beetroot juice supplementation resulted in training-induced improvements in VO_{2peak} of 7.7 to 10.7% [85, 75], which were greater than with SIT alone (+5.6%) or after SIT with potassium NO_3^- (KNO_3) supplementation (+4.2%) [85]. Time-to-fatigue during high-intensity cycling (power at the gas exchange threshold plus 85% of the difference between

that work rate and VO_{2peak}) also improved more with SIT+ beetroot juice (+71%) compared to SIT alone (+47%) and SIT+KNO_3 (+42%) [85]. Greater reductions in blood pressure were observed with SIT+ beetroot juice compared with SIT+KNO_3, a disparity that has also been reported between the ingestion of beetroot juice and $NaNO_3$ [88] and may be related to the presence of other bioactive compounds found in beetroot juice [89]. Though speculative, the greater decrease in plasma NO_2^- observed during exercise with SIT+ beetroot juice compared with SIT+KNO_3 may suggest enhanced NO synthesis during exercise, and is in accordance with observed correlations between the decline in plasma NO_2^- and improvements in exercise performance [90]. Two of the training studies used $NaNO_3$ as the source of nitrate (6.5 and 11 mmol per day), and neither found any additional performance improvements [77, 87]. Further research should examine the effects of supplementation with different dietary nitrate sources on adaptations to endurance training.

Similar to buffering agents, dietary nitrate works primarily on peripheral metabolism and short-term intake would not be expected to have an appreciable influence on VO_{2peak}. One explanation for the observed improvements in VO_{2peak} may be related to changes in muscle fibre type. The percentage of slow-twitch fibres is directly related to VO_{2peak} and endurance performance [91, 92], and the two studies that showed an additional increase in VO_{2peak} with supplementation also found changes in fibre-type composition [75, 85]. A decreased proportion of type IIx muscle fibres in the vastus lateralis was observed in the nitrate group compared with placebo [75], and there was a greater increase in the proportion of type IIa fibres after both SIT alone (+20%) and SIT+ beetroot juice (+14%), compared with SIT+KNO_3 (non-significant decrease) [85]. It is unclear if these differences suggest that

SIT+KNO_3 is not as effective as SIT alone, or if this highlights the variability and/or reliability of fibre-type measures, which are reported to have inter-biopsy coefficient of variations of 21.5, 15.4 and 42.0 % for type I, IIa and IIx fibres, respectively [93]. Five weeks of SIT in hypoxia with $NaNO_3$ supplementation also increased the relative number of type IIa fibres, which was not observed with placebo supplementation in either normoxia or hypoxia, although similar improvements between groups were seen in VO_{2max}, the lactate threshold, and CS activity [77]. This is in accordance with *in vitro* research showing nitrate increased *PGC-1*α gene expression and a switch toward type I and IIa muscle fibres [94].

Two studies have examined the effects of dietary nitrate on training adaptations one to seven days after stopping supplementation [95, 87]. Twenty-eight days of NO_3^- supplementation in recreationally-active participants who maintained their typical exercise habits was followed by exercise testing after one day of placebo or continued nitrate in order to study chronic + acute vs. chronic-only dosing [95]. There was a reduction in the oxygen cost of submaximal cycling even up to 24 h after consuming the final dose of NO_3^-, which was similar to what was observed after 28 days of supplementation followed by an acute dose of NO_3^- prior to testing [95]. There are several potential reasons for this observation, including lasting improvements in mitochondrial [71] or muscle contractile efficiency [72] from chronic supplementation, or that in spite of plasma nitrite concentrations returning to baseline after 24 h NO bioavailability remained elevated as a result of stored NO_2^- and NO_3^- in skeletal muscle [96]. Another study investigated three weeks of high-volume HIIT in recreationally-active participants consuming either ~11 mmol $NaNO_3^-$ per day or a placebo, who performed a series of exercise tests two to seven days after the final day of supplementation [87]. Total

oxygen consumption decreased by 5% in the supplement group but not the placebo group during a time to exhaustion test at 80% W_{max} that was performed 4 to 5 days after cessation of supplementation, although no differences were seen between groups for improvements in the time itself or in VO_{2peak} [87]. Overall, limited data suggest the beneficial effects of NO_3^- supplementation on oxygen consumption during submaximal exercise may continue to be observed for up to 5 days, but mechanisms and the exact time-course of washout remains to be elucidated.

3.1 Summary

The limited evidence suggests there may be small but favourable effects of endurance training with nitrate supplementation, which are possibly related to changes in muscle fibre-type. Beetroot juice may be more effective than nitrate salts, though the efficacy of supplementation can be affected by inter-individual variability [97] and environmental conditions [98]. All studies to date have used high-intensity training protocols, as dietary nitrate is particularly effective at augmenting physiological responses in type II fibres [99]. Studies using other forms of endurance training are needed to differentiate acute ergogenic benefits from the chronic effects of dietary nitrate on training adaptations. More research is required to determine the role of nitric oxide on mitochondrial biogenesis [74], as well as to investigate differences in the skeletal muscle remodeling responses - particularly between untrained and endurance-trained participants (Table 2).

4. Antioxidants

Free radicals are produced during aerobic metabolism and play a role in both exercise-induced fatigue and the adaptive response to exercise [100]. Muscle contractile force is decreased by elevated levels of reactive oxygen and nitrogen species (RONS), largely due to changes in myofibrillar calcium sensitivity [101]. At the same time, RONS generated during exercise act as signaling molecules to increase the production of proteins involved in the skeletal muscle adaptation to exercise such as NO synthase, superoxide dismutase (SOD), and MAP kinases p38, ERK1 and ERK2 (Fig. 2) [102, 103]. For example, RONS, via AMPK activation, can induce PGC-1α promoter activity and mRNA expression [104]. Due to their effects of reducing RONS, antioxidants have the potential to impair the adaptive responses to RONS-induced stressors and therefore negate favourable training adaptations that would normally occur [105], while also having the potential to improve recovery and acute performance [106-108]. Some antioxidants, including polyphenols, may exert their effects in areas beyond RONS signaling, such as increased mobilisation of fatty acids [109] or sirtuin 1 (SIRT1) activation (Fig. 2) [110]. For additional discussion of the effects of antioxidant supplementation on exercise performance the reader is referred to recent reviews [14, 105, 111].

4.1 Vitamins C and E

Vitamins C and E are antioxidant vitamins with a role in protecting cellular organelles from oxidative damage [112, 113]. No impact on exercise performance outcomes has been observed in human studies when supplementing with vitamins C and/or E during controlled endurance training [114-125] (Table 4). Skeletal muscle adaptations, such as training-induced increases in CS or β-HAD enzyme activity, mRNA or protein levels of cytochrome c

oxidase subunit IV (COX-IV), heat shock protein 70, or changes in substrate oxidation, have not been affected by supplementation in healthy participants after 4 to 12 weeks of training [120, 123-126]. In contrast, supplementation with vitamins C and E for 4 to 11 weeks has blunted training-induced increases in COX-IV, PGC-1α, PGC-1β, PPARγ, SOD, and GPx protein compared with a placebo in both untrained and previously-trained participants [122, 127]. Animal studies have also shown that 4 to 14 weeks of aerobic training with antioxidant intake blunted training-induced increases in cytochrome oxidase and CS activity, mitochondrial transcription factor A (TFAM), CYT-C, GPx, glutathione reductase, SOD, PGC-1α, NRF-1, and NRF-2 [118, 128-130], although other research has shown no effect on markers of training adaptations such as mitochondrial respiratory capacity, and CYT-C, COX-I, COX-IV, CS, NRF-1, or PGC-1α protein content [130-133].

The reason for these divergent findings, particularly in the animal research, may be due to variations in dosing, exercise protocols, and baseline levels of endogenous antioxidants. The amount of antioxidant provided has varied more than 10-fold [128, 134], exercise type has included both running and swimming, and the duration of training sessions has ranged from 30 min to six hours per day [132-134]. Potential redundancies in the adaptation process must also be considered. For example, contracting skeletal muscle activates AMPK via its upstream kinase Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) [135], and changes in proteins regulating fat metabolism such as FAT/CD36 are mediated in part by contraction-induced signaling of the ERK1/2 pathway [136]. Thus, many of the common adaptations to endurance training may be observed in the absence of RONS signaling and be minimally influenced by antioxidant supplementation.

It should also be considered that some effects may be missed due to small sample sizes. For example, the two human studies showing a blunting of training adaptations with antioxidant supplementation also had the largest sample sizes [122, 127]. In contrast, eight weeks of endurance training with or without supplementation had no statistical effect on increases in VO_{2max}, but the vitamin C group (n=5) improved by 10.8% while the group without supplementation (n=9) improved by 22% (*d* = -1.0) [118].

The effects of vitamins C and E supplementation on markers of oxidative stress have also been variable, with reports of reductions [116], increases [119, 137], and no impact [123, 138]. This may be primarily related to methodological issues including the use of assays that are no longer recommended, short half-lives of oxidants being measured, and lack of measurement specificity, making both conducting and interpreting the available research difficult [139-141]. More research is needed before a conclusion can be drawn regarding the impact of vitamins C and E on markers of oxidative stress during endurance training.

4.2 Polyphenols

Polyphenols are antioxidants found in plants, with the potential to impact chronic adaptations to endurance training by several mechanisms that differ from the antioxidant effects of vitamins C and E. Rather than acting as scavengers, they can stimulate stress-related cell signaling pathways and increase the expression of genes encoding proteins, such as NRF2, as well as by stimulating the SIRT1–AMPK–PGC1α pathway in skeletal muscle, leading to increased mitochondrial biogenesis (Fig. 2) [142]. Perhaps, paradoxically for the

endurance athlete, it is thought that AMPK activation relies on the ability of polyphenols, such as quercetin and resveratrol, to directly bind and inhibit the mitochondrial F1F0-ATPase/ATP synthase (Complex V), thus impairing ATP production [143]. A number of studies have investigated the effect of polyphenols on exercise performance [142]; however, there are few that have also included supervised endurance training programs (Table 4).

4.2.1 Resveratrol

Resveratrol is a polyphenol found in grapes, red wine, and other plant species and is known to activate SIRT1 [110], and can shift muscle fibres towards a more oxidative phenotype [144]. Resveratrol supplementation during eight weeks of HIIT in sedentary men blunted the training-induced improvements in VO_{2max} and protein carbonylation, while having no effect on *PGC-1α* mRNA, CYT-C, CS and β-HAD activity, or time to exhaustion during a one-legged knee-extensor test, compared with a placebo [145, 146]. In contrast, four weeks of resveratrol supplementation by recreationally-active men performing HIIT resulted in no differences in training-induced increases in VO_{2max}, peak aerobic power, Wingate power, succinate dehydrogenase activity, or fibre-type distribution, compared to placebo, although the resveratrol group had smaller increases in the gene expression of *PGC-1α*, *SIRT1*, and *SOD* [147]. This is in line with *in-vitro* research showing acute exposure to resveratrol inhibits AMPK activity in human skeletal muscle cells [148]. Following 12 weeks of treadmill training with resveratrol, rats bred for increased endurance capacity had increased activation of the AMPK-SIRT1-PGC-1α pathway and VO_{2max} [149], while rats bred for low aerobic capacity had no differences in VO_{2max}, AMPK, or SIRT1 levels [150], suggesting the response to resveratrol may be influenced by training status. The available data on

resveratrol are limited but suggest that active/trained humans and animals may respond differently than those who are sedentary/untrained.

4.2.2 Green Tea Extract

Green tea extracts are a type of polyphenolic flavonoids which, beyond their role as an antioxidant, may also play a role in the mobilisation and oxidation of fatty acids [151] that appears to be mediated, at least in part, by reducing the malonyl-CoA content in skeletal muscle [152]. Supplementing green tea extract during ten weeks of moderate-intensity endurance training in healthy males resulted in greater fat oxidation while cycling at 55% VO_{2peak}, with no changes observed in the placebo group [109] (Table 4). Untrained men who performed a 4-week training intervention with green tea extract or placebo had similar improvements in VO_{2max} and run to exhaustion time (8.1–9.7 km/h at 18-20% grade), with no differences between groups for total antioxidant status [153]. However, these are performance tasks that would not be expected to benefit from increased fat oxidation rates as they are at an intensity that would be reliant on carbohydrate oxidation [154]. Mice that underwent endurance training for 10 weeks with green tea extract supplementation had better running (~2.5 h) and swimming (~40 min) times to exhaustion compared with the exercise-only group, along with higher levels of muscle β-oxidation and *FAT/CD36* mRNA [152, 155]. The limited data examining green tea extract in the context of endurance training support the notion of increased fat oxidation and improvement in exercise time to exhaustion in animals but not untrained men; however, studies that include other measures of performance (e.g. time-trials) are needed, particularly at intensities and durations that may favour improved fat oxidation.

482

483 *4.3 Other Antioxidants*

484 Supplementation with (-)-epicatechin, a component of cocoa known to activate the SIRT1
485 pathway [156], impaired training adaptations during four weeks of cycling training;
486 increases in VO_{2peak} (+22.6%) and succinate dehydrogenase activity (+59.1%) were seen in
487 the placebo but not the supplement group, although no differences in peak power or CS
488 activity were observed between groups [157] (Table 4). In contrast, mice undergoing
489 treadmill training had greater increases in time to exhaustion, CS levels, and protein levels
490 of PGC-1β and TFAM with (−)−epicatechin supplementation compared with exercise-only
491 [158]. The use of allopurinol (an inhibitor of xanthine oxidase) in rats for six weeks had no
492 effect on training-induced increases in PGC-1α, TFAM, or CYT-C protein expression, or CS
493 and β-HAD enzyme activity, despite an attenuation of key signaling proteins (p38 MAPK,
494 ERK1/2, and TFAM) after a single session of exercise [103, 159], highlighting the importance
495 of studying longer-term adaptations to endurance training.

496

497 *4.4 Summary*

498 Endurance-related performance improvements following one- to six-month training
499 programs are not impacted by supplementation with vitamin C and/or vitamin E and are
500 unlikely to be affected by other antioxidants, although fewer data are available. Less clear
501 are the effects of vitamins C and E on markers of training adaptations and oxidative stress.
502 The disconnect between an impaired adaptive response without measurable performance
503 decrements may imply that longer time frames are needed before observable differences in
504 performance can be detected. Differences in training protocols, training status, and type and

amount of supplementation, may also be responsible for contrasting results, as well as inherent redundancy in the mechanisms governing skeletal muscle adaptations to exercise. ROS production is only one of the mechanisms by which adaptation is regulated, along with contraction-induced changes in mechanical strain, ATP turnover, calcium flux, redox balance, and intracellular oxygen pressure (Fig. 2) [3]. Although many studies report attenuated levels of signaling molecules involved in mitochondrial biogenesis, increased levels of CS activity suggest that changes in mitochondrial volume are not inhibited by antioxidant supplementation [123, 159]. Future research should attempt to differentiate between the antioxidant actions of a given supplement and other signaling pathways (e.g. AMPK, SIRT1) that may be influenced.

5. Caffeine

Caffeine is well-studied and commonly reported to exhibit performance-enhancing effects during endurance exercise [160]. When taken in moderate doses (3 to 6 mg/kg), 2 to 3% improvements are seen in time-trial performance lasting 6 min to 2.5 h [160] and power during HIIT [161]. It has been suggested that habitual caffeine usage will decrease its efficacy [162]. However, caffeine supplementation (4 to 6 mg/kg) has improved 30- to 45-min cycling time-trial performance in habitual low, moderate, and high caffeine consumers [163, 164], and the ingestion of 3 mg/kg for 20 days continued to produce an ergogenic effect [165], suggesting that regular caffeine consumption during training sessions should not reduce its longer-term impact. Despite its widespread use, little is known about the effects of caffeine ingestion prior to exercise on subsequent adaptations to training.

There are several mechanisms that could lead to enhanced endurance training adaptations. By way of reduced perception of exertion, likely through its effects as an adenosine receptor antagonist [166], an athlete may be able to accumulate a greater training stress. Indeed, participants who consumed 3 to 6 mg/kg caffeine completed 12.6% more work during 30 minutes of cycling at a given level of perceived exertion [167], increased power by 2.8% during HIIT (8x5 min at maximum intensity with 1 min recovery) [161], and were able to mitigate reductions in power during training sessions performed with low carbohydrate availability [161]. Caffeine can increase exogenous carbohydrate oxidation [168], possibly via greater intestinal absorption [169], and also increase AMPK activation via calcium-mediated protein phosphatase 2A activity [170]. Emerging research also points to a role for caffeine in improving mitochondrial respiration via its effects on mitochondrial p27 [171], suggesting the potential to work synergistically with SIT - the form of interval training that has been associated with the greatest improvements in mitochondrial respiration [172]. Taken together, caffeine has the potential to impact training adaptations across a number of key pathways that can ultimately lead to greater increases in mitochondrial biogenesis (Fig. 2).

Despite the above rationale, only one study in humans, and one study in rats, has investigated the effects of caffeine on adaptations to endurance training. In the human study, the caffeine was part of a multi-ingredient supplement, dietary caffeine intake was not controlled for, and there were no differences in caffeine consumption between groups [173], while rats given caffeine prior to each exercise session during six weeks of HIIT were only studied for changes in brain and behavioral biomarkers [174]. Research should investigate the effects

of caffeine on training adaptations, in conjunction with the impact of exercise intensity, training status [175], sex [176], and genotype [177], using moderate (3 to 6 mg/kg) and low (<3 mg/kg) [178] doses.

6. Creatine

Though creatine supplementation is rarely associated with endurance sports, it has been shown to enhance exercise performance across a variety of sporting events (e.g. sprinting, middle-distance, team sports, and HIIT in endurance sports [179]) and this has been attributed to elevated muscle content of creatine and phosphocreatine [179]. A dose of 5 g four times per day for 5 to 7 days is commonly used as a loading protocol, with subsequent daily doses of 3 to 5 g/day to maintain elevated creatine levels [179]. However, high and low responders to creatine supplementation have been identified, possibly due to variations in baseline muscle creatine content [180], and/or its uptake and use [181]. Despite the accepted role of creatine for improving performance, there has been little investigation of its ability to affect adaptations to training.

There are several potential mechanisms by which creatine supplementation may be able to affect training adaptations. Exercise intensity appears to be a key factor for training-induced increases in mitochondrial respiration [172], and so any supplement that can increase exercise intensity could potentially offer additional benefit to endurance training, adaptation, and performance. In addition to its primary role of combining with a phosphoryl group to form phosphorylcreatine via the creatine kinase reaction, creatine may also play a role in aerobic energy metabolism by connecting sites of ATP production (glycolysis and

574 oxidative phosphorylation) with subcellular sites of ATP utilisation (ATPases) [182], with
575 subsequent enhancement of mitochondrial respiration in slow-twitch but not fast-twitch
576 fibres [183]. This may allow a greater amount of work to be completed during a training
577 session, and a reduced oxygen cost during submaximal exercise. Creatine has also been
578 shown to have antioxidant actions reducing the formation of ROS, oxidative DNA damage,
579 and lipid peroxidation after exercise, which may affect exercise-induced cell signaling [184].
580 There is a potential for increases in body mass due to water retention with creatine loading
581 [179]. However, despite a ~2.5% increase in body mass, well-trained cyclists undergoing
582 both creatine and carbohydrate loading reported a greater power output during sprint
583 efforts within a simulated 120-km time trial, with no differences in simulated uphill cycling,
584 compared to placebo [185].
585
586 Two studies using recreationally-active men performing four weeks of HIIT while
587 supplementing with either creatine (10 g/day) or a placebo reported significant
588 improvements in the creatine but not placebo groups for critical power and ventilatory
589 threshold (Table 5) [186, 187]. However, no differences were seen between groups for
590 VO_{2peak}, time to exhaustion at VO_{2peak}, anaerobic working capacity, or total work done during
591 a ride to exhaustion at 110% of peak aerobic power [186, 187]. Similar research in
592 recreationally-active women found no differences in exercise-induced improvements in
593 VO_{2peak}, ventilatory threshold, or 2-km time-trial performance (~2 min) [188]. However, that
594 study did not match menstrual phase, which has been shown to impact the blood lactate
595 response to high-intensity exercise [189]. Similar to other supplements, it is difficult to
596 separate the effects of creatine on performance from its effects on adaptations to training.

For example, in the absence of training, 5 to 7 d of creatine loading resulted in increases in power at the lactate threshold [190] and supra-maximal time to exhaustion [190, 191], as well as lower VO_2 during sub-maximal cycling [191]. Thus, while creatine may improve some adaptations to endurance training, the limited evidence does not yet support its widespread use by endurance athletes. More research is needed, particularly in trained participants performing 15-s to 4-min intervals using maximal efforts rather than pre-determined work rates, while also controlling for the effects of the supplement alone (Table 2).

7. Conclusion

The most important variables impacting adaptations to endurance training are the training stimuli - volume and intensity. However, within a given training paradigm, the appropriate use of dietary supplements may offer additional benefits. These benefits appear largely by allowing increasing training intensities, and so HIIT prescriptions should avoid pre-determined workloads in favor of time-based intervals (e.g. 4-min maximal efforts). Beetroot juice appears to impact skeletal muscle fibre-type remodeling, though more research with concurrent endurance training is needed. Supraphysiological doses of antioxidants should be used with caution as research is unclear regarding the extent of their effects on training adaptations, but they appear unlikely to negatively affect performance in the short-term (< 6 months). Caffeine and creatine have potential for augmenting adaptations to endurance training, although clear data are lacking.

Finally, it is imperative for athletes who compete under anti-doping rules to avoid supplements that contain prohibited substances [192]. It is tempting to interpret small or

620 trivial effects in sport science research as unlikely to harm, but the risk of positive doping
621 tests should be weighed against the unproven effects of a supplement. Clearly, strong caution
622 must be used when athletes, coaches, and health care practitioners are selecting dietary
623 supplements for use.

Table 1: Overview of studies using buffering agents during supervised endurance training

	Participants	Training Status	Length	Supplement Dosage	Type of Training	Total Number of Training Sessions	Performance (compared with placebo)	Adaptations (compared with placebo)
Sodium Bicarbonate								
Edge et al. 2006[33]	16 f	Recreationally Active	8 weeks	0.4 mg/kg body mass	HIIT 3x/wk; 6-12x 2-min cycle intervals at 140 – 170% of LT, 1 min RBI	24	Lactate threshold (LT): +26 vs. 15% (*d*= 0.5, [95% CI -0.5, 1.5]) Time to fatigue: +164 vs. 123% (*d*= 1.9, [95% CI 0.7, 3.1]) No difference in or $VO_{2\ peak}$	No differences in muscle buffer capacity
Driller et al. 2013[36]	12 m	Well-Trained	4 weeks	0.3 g/kg body mass	HIIT 2x/wk; 8 × 2.5-min rowing intervals at 90% of PPO, 3 min RBI	8	No differences in performance or LT	
Hawke et al. 2014[35]	19 m	Recreationally Active	6 weeks	0.4 g/kg body mass	HIIT 3x/wk; 8-12x 2-min cycling intervals at 85-110% VO_{2peak}, 1 min RBI	18	No differences in performance or LT	CS activity +22.3 vs. 12.6%
Wang et al. 2019[34]	20 m	Recreationally Active	6 weeks	0.2 g/kg body mass	HIIT 3x/wk; 4 sets of 20-30 s cycling at 100% PPO, 30-40 s at 70% PPO, 1 min RBS	18	Greater improvement in Wingate relative peak power (20.8 vs. 10.3% (*d* = 2.1, [95% CI 1.0, 3.2]) No differences in Wingate relative mean power	Increased peak lactate concentration only in the sodium bicarbonate group
Bishop et al. 2010[37]	21 m rats	N/A	5 weeks	0.05 g/kg body mass	HIIT 5x/wk; 7-12 x 2 min treadmill intervals, 1 min RBI	25	Time to fatigue: 12-fold vs. 8-fold longer than control (*d*= 11.1, [95% CI 6.8, 15.3])	Greater improvements in mitochondrial mass and respiration (*d*= 1.8, [95% CI 0.6, 3.1])
Beta-alanine								
Smith et al. 2009[57]	46 m	Recreationally Active	6 weeks	3 weeks at 6 g/day followed by 3 weeks at 3 g/day	HIIT 3x/wk; 5-6x 2-min cycle intervals at 90-115% PPO, 1 min RBI	18	No difference in $VO_{2\ peak}$ Time to exhaustion at 110% PPO: +18.7 vs. 15.1% (*d*= 0.3, [95% CI -0.4, 0.9])	
Walter et al. 2010[54]	44 f	Recreationally Active	6 weeks	3 weeks at 6 g/day followed by 3 weeks at 3 g/day	HIIT 3x/wk; 5x 2-min cycle intervals at 90-110% PPO, 1 min RBI	18	No difference in VO_{2max} or power at ventilatory threshold	
Bellinger et al. 2012[61]	14 m	Well-Trained	4 weeks	65 mg/kg body mass/day	HIIT 2x/wk; 8 x 2.5 min cycling intervals at 90% VO_{2max} HR	8	No differences in 4-min time-trial power	

Howe et al. 2013[59]	16 m	Well-Trained	4 weeks	4.5 g/day	HIIT 2x/wk; 8x 2.5 min at 90%PPO, 3 min RBI	8	No differences in 4-min time-trial power, trend for increased total work done (p=0.09)	
Cochran et al. 2015[55]	24 m	Recreationally Active	6 weeks	4 weeks loading with 3.2 g/day, followed by 6 weeks of 3.2 g/day with supervised training	SIT 3x/wk; 4–6 Wingate tests, 4 min RBI	18	No difference in VO_{2peak}, repeated-sprint capacity, or time trial performance	No difference in cytochrome-c oxidase or β-HAD maximal activities
Bellinger and Minahan 2016[53]	14 m	Well-Trained	5 weeks	4 weeks loading with 6.4 g/day, followed by 5 weeks of 1.2 g/day with supervised training	SIT 2x/wk; 4-6x 1-km (~1.3 min) cycling sprints, 4 min RBI	10	No difference in TT performance or VO_{2max} Training intensity: +9.9 vs. 4.9% (*d*= 0.3, [95% CI -0.8, 1.3]) Time to exhaustion at 120% PPO: +14.9 vs. 9.0% (*d*= 0.5, [95% CI -0.6, 1.58])	
Santana et al. 2018[58]	16 m	Recreationally Active	23 days	5 g/day	Moderate intensity 2x/wk (7-12 km), HIIT 1x/wk (6x500 m sprints, 2 min RBI)	9	10 km running performance: -6.7% vs. no change	
Wang et al. 2018[56]	38 m	Recreationally Active	4 weeks	6.4 g/day	HIIT 2x/wk; three sets of 5x10 s maximal sprints, 20 s RBI, 5 min RBS	8	No difference in VO_{2max} or PPO Anaerobic capacity: 14% higher than placebo (*d* = 0.8, [95% CI -0.1, 1.8])	

HIIT: High-intensity interval training, SIT: sprint-interval training, TTE: Time to exhaustion, PPO: Peak power output, RBI: Rest between intervals, RBS: Rest between sets

Effect size of supplement calculated as Cohen's d when data were available (reported as effect size, 95% CI)

Table 2. Proposed mechanisms and recommendations for studying endurance training adaptations

	Mechanisms of action	Ingestion	Type of training	Outcome measures
Sodium bicarbonate	- Increased training intensity - Increased pH --> improved mitochondrial adaptations	0.2-0.4 g/kg body weight - sufficient to raise blood [$HCO3^-$] by 5-6 mmol	Interval training sufficient to elevate lactate levels and/or pH compared with a placebo	- Lactate threshold - Mitochondrial mass and respiration - Time to fatigue at maximal or near-maximal efforts - Time-trial performance
Beta-alanine	- Increased training intensity - Increased pH --> improved mitochondrial adaptations - Improved Ca sensitivity - Reduced lipid peroxidation	2-4 wk loading phase of 4-6 g/d, followed by 3-6 g/d	1 to 4 min intervals using maximal efforts rather than pre-determined work rates, sufficient to elevate blood lactate compared with a placebo	- Open-ended exercise tests (e.g. time to exhaustion) rather than fixed end-point tasks (e.g. time trials) - Training intensity - Oxidative stress
Dietary nitrate	- Increased training intensity - Increased mitochondrial biogenesis via nitric oxide signaling and possibly RONS - Reduced oxygen cost - Muscle fibre-type remodeling	8-13 mmol/d from beetroot juice	15 s to 4 min intervals using maximal efforts rather than pre-determined work rates, steady-state endurance	- Mitochondrial mass and respiration - Muscle fibre-type changes - Training intensity - VO_{2max}
Antioxidants	- Reduced oxidative stress leading to improved training and recovery - Stimulate or impair stress-related signaling pathways Stimulate mitochondrial biogenesis	More research needed before recommendations can be made, particularly with regard to timing relative to exercise	More research needed before recommendations can be made	- Mitochondrial adaptations - Performance changes - Training intensity
Caffeine	- Increased training intensity via decreased perception of exertion - Improved Ca sensitivity - Increased AMPK signaling	2-6 mg/kg	0.5 to 4 min intervals using maximal efforts rather than pre-determined work rates	- Mitochondrial mass and respiration - Training intensity
Creatine	- Increased training intensity - Improved energy production - Reduced lipid peroxidation	10 g/d for 10 d, then 10 g/d on training days only - more research needed	15 s to 4 min intervals using maximal efforts rather than pre-determined work rates	- Mitochondrial respiration - Training intensity - Time-trial performance

626

Table 3: Overview of studies using dietary nitrate during supervised endurance training

	Participants	Training Status	Length	Supplement Dosage	Type of Training	Total Number of Training Sessions	Performance (compared with placebo)	Adaptations (compared with placebo)
Puype et al. 2014[83]	22 m	Moderately Trained	6 weeks	~5 mmol per day (0.07 mmol NO_3^-/kg body mass)	30 min at 4-6 mmol/L blood lactate, 5x/wk in normobaric hypoxia	30	No difference in VO_{2max}, LT, or time-trial performance	
De Smet et al. 2016[77]	27 m	Recreationally Active	5 weeks	6.5 mmol $NaNO_3$	SIT 3x/wk in normobaric hypoxia; 4-6 Wingate tests, 4.5 min RBI	15	No difference in VO_{2max}, LT, or time-trial performance	Increased percentage of type IIa fibres No difference in CS activity
Muggeridge et al. 2017[84]	27 m	Recreationally Active	3 weeks	~8 mmol nitrate [0.06–0.15 mmol/kg body mass]	SIT 3x/wk; 4-6x 15 s maximal sprints, 4 min RBI	9	Maximal work rate during incremental exercise: +8.7 vs. 4.7% (*d*= 0.3, [95% CI -0.6, 1.2]) No difference in VO_{2max}	
Thompson et al. 2017[75]	18 m, 18 f	Recreationally Active	4 weeks	12.8 mmol NO_3^- per day (2 servings of 6.4 mmol, AM/PM)	SIT 3-4x/wk; 4-5 Wingate tests, 4 min RBI	14	VO_{2peak}: +8.8 vs 2.0% (*d*= 0.2, [95% CI -0.6, 1.0]) Maximal work rate during incremental exercise: +7.7 vs. 5.0% (*d*= 0.1, [95% CI -0.7, 0.9]) No difference in time to fatigue at high intensity	Decreased proportion of type IIx muscle fibres in the vastus lateralis
Thompson et al. 2018[85]	18 m, 12 f	Recreationally Active	4 weeks	12.8 mmol NO_3^- per day (2 servings of 6.4 mmol, AM/PM)	SIT 3-4x/wk; 4-5 Wingate tests, 4 min RBI	14	$VO_{2\ peak}$: +10.7 vs. 5.6% (*d*= 0.2, [95% CI -0.7, 1.0]) Time to fatigue: +71 vs. 47% (*d*= 0.4, [95% CI -0.5, 1.3]) No difference in maximal work rate during incremental exercise	
Finkel et al. 2018[87]	17 m	Recreationally Active	3 weeks	~11 mmol per day (0.14 mmol $NaNO_3^-$ /kg body mass)	HIIT 3x/wk; 45 intervals of 30 s at 10 w below Wmax, 30 s recovery at 10 w	9	No differences in VO_{2max}, W_{max}, or time to exhaustion at 80% W_{max} Only placebo increased power during first of a dual Wingate test (6%; *d*= -0.5, [95% CI -1.4, 0.5), similar improvements for second test	
Santana et al. 2019[86]	16 m	Recreationally Active	4 weeks	~12 mmol per day (across three servings)	Moderate intensity 2x/wk (5-12 km), HIIT 1x/wk (4-6x500 m sprints, 2 min RBI), weekly 10-km time-trial	12	"10-km running time: -9.1 vs. -1.0% (d = 1.2, [95% CI -2.3, -0.2]) No differences in 60-s Wingate test"	Lower lactate during 10-km time-trial

HIIT: High-intensity interval training, SIT: sprint-interval training, TTE: Time to exhaustion, PPO: Peak power output, RBI: Rest between intervals, W_{max}: Maximal aerobic wattage

Effect size of supplement calculated as Cohen's d when data were available (reported as effect size, 95% CI)

629 Table 4: Overview of studies using antioxidant supplements during supervised endurance training

Humans	Supplement	Supplement Dosage	Participants	Training Status	Length	Type of Training	Total Number of Training Sessions	Performance (compared with placebo)	Metabolic Adaptations (compared with placebo)	Oxidative Stress (compared with placebo)
Sharman et al. 1971[114]	Vitamin E	400 mg	26 m	Trained	6 weeks	4x/wk Competitive swim training - unspecified	24	No difference in 1 mi run or 400 m swim times		
Lawrence et al. 1975[115]	Vitamin E	900 iu	48	Well-trained	6 months	Competitive swim training - unspecified	Unspecified	No difference in 500 yd or 100 yd swim times		
Rokitzki et al. 1994[116]	Vitamin E	330 mg	30 m	Well-trained	5 months	Competitive cycling training - unspecified	Unspecified	No difference in LT		Reduced MDA
Oostenbug et al. 1997[117]	Vitamin E and fish oil	300 iu	24 m	Well-trained	3 weeks	Competitive cycling training - unspecified	Unspecified	No difference in VO_{2max}, maximal workload, or 1-hr time-trial		
Gomez-Cabrera et al. 2008[118]	Vitamin C	1000 mg	14 m	Sedentary	8 weeks	3x/wk; 40 min steady-state cycling at 65-80% VO2max	24	Trend for smaller improvement in VO_{2max}: +10.7 vs. 22% (*d*= -1.1, [95% CI -2.2, 0.04])		
Roberts et al. 2011[120]	Vitamin C	1000 mg	15 m	Recreationally Active	4 weeks	4x/wk HIIT; 5x3 min treadmill running at 90% VO2max, 3 min RBI	16	No difference in VO_{2max} or 10-km time-trial performance	No difference in substrate utilization	
Braakhuis et al. 2014[119]	Vitamin C	1000 mg	23 f	Trained	3 weeks	3x/wk running; 4x 3-5 min and 6x2 min hill repeats	10	No difference in 5-km time trial		Increased protein carbonyl at rest, increased SOD post-exercise, blunting training-induced decrease in resting CAT activity
Bryant et al. 2003[121]	Vitamin C and E	1000 mg vit C, 400 iu/kg vit E, or 1000 mg vit C + 200 iu/kg vit E	7 m	Trained	3 weeks	Competitive cycling training, 250–350 km/wk	Unspecified	No difference in work completed	No difference in substrate oxidation	Vit C Increased MDA, no difference with vit C+E
Ristow et al. 2009[127]	Vitamin C and E	1000 mg vit C, 400 iu vit E	39 m	Trained and Untrained	4 weeks	5x/wk; 20 min biking or running, 45 min circuit training	20		Decreased PGC-1a, PGC-1β, PPARγ, SOD, and GPx	

Yfanti et al. 2010,[123] 2011[124]	Vitamin C and E	500 mg vit C, 400 iu vit E	21 m	Recreationally Active	12 weeks	5x/wk cycling; one day each of graded exercise test; 10x3 min at 85% PPO, 3 min RBI; 1x60 min at 60% PPO; 5x8 min at 75% PPO, 4 min RBI; 1x120 min at 55% PPO	60	No difference in VO_{2max}, maximal workload, or LT	No difference in CS, β-HAD, PGC-1a, or PPARγ	No difference in SOD
Paulsen et al. 2014 [122] Cumming et al. 2014[126]	Vitamin C and E	1000 mg vit C, 235 mg vit E	26 m, 28 f	Trained	11 weeks	3-4 w/wk running; 2 days steady state 30-60 mins at 72-87% HR max, 2 days 4-6 x 4-6 min >90% HR max	41	No difference in VO_{2max} or shuttle run test	Decreased PGC-1α and COX-IV	Decreased uric acid No difference in GPx, SOD, GSH, or HSP70
Morrison et al. 2015[125]	Vitamin C and E	1000 mg vit C, 400 iu vit E	11 m	Recreationally Active	4 weeks	3x/wk cycling, 10x4 min at 90% VO2max, 2 min RBI	12	No difference in VO_{2max}	No difference in CS or COX-IV Decreased TFAM	Decreased SOD
Shill et al. 2016[193]	Coenzyme Q10	10 mg MitoQ (proprietary CoQ-10)	20 m	Recreationally Active	3 weeks	3-5x/wk cycling, 45-60 min at 50-70% VO2max	13	No difference in VO_{2max}	No difference in mitochondrial function	No difference in MDA
Ichinose et al. 2011[109]	Green tea extract	578 mg tea catechins	20 m	Recreationally Active	10 weeks	3x/wk cycling, 60 min at 60% VO2max	30		Increased fat utilization	
Kuo et al. 2015[153]	Green tea extract	207 mg tea catechins	40 m	Sedentary	4 weeks	3x/wk running, 20 min at 75% oxygen uptake reserve	12	No difference in VO_{2max} or time to exhaustion		No difference for MDA or total antioxidant status
Scribbans et al. 2014[147]	Resveratrol	150 mg	16 m	Recreationally Active	4 weeks	3x/wk HIIT cycling, 8x20 s at 170% PPO, 10 s RBI	12	No difference in VO_{2max}, peak aerobic power, or Wingate power	No difference in succinate dehydrogenase activity Decreased gene expression of PGC-1a, SIRT1, and SOD	
Gliemann et al. 2013 [145] Oleson et al. 2014 [146]	Resveratrol	250 mg	27 m	Sedentary	8 weeks	2x/wk HIIT cycling, 1x/wk Crossfit (unspecified)	24	Smaller increase in VO_{2max}: +12.8 vs. 17.2% (*d*= -1.4, [95% CI -2.2, -0.5]) No difference in time to exhaustion	No difference in on PGC-1a mRNA, CYT-C, CS and β-HAD activity	Increased protein carbonyls
Polley et al. 2016[194]	Resveratrol	500 mg Resveratrol + 10 mg piperine	9 m, 7 f	Recreationally Active	4 weeks	3x/wk, 30 min forearm wrist flexor exercises	12		Increased mitochondrial oxidative capacity	
Schwarz et al. 2018[157]	Epicatechin	200 mg	20 m, f	Recreationally Active	4 weeks	4x/wk cycling, 2x 45-60 min at 50% W_{max}, 1x/wk HIIT, 1x/wk SIT	16	Smaller increase in VO_{2max}: +6.1 vs. 22.6% (*d* = -0.6, [95% CI -1.5,	Only placebo increased succinate	

								0.4]), no difference in peak aerobic power	dehydrogenase activity (+59%)	
Animals										
Venditti et al. 2014[128]	Vitamin E	700 mg/kg	32 m	Rats	10 weeks	5x/wk; 15-60 min/d swimming	50		Decreased mitochondrial respiration, NRF-1, NRF-2, PGC-1	Increased protein carbonyls Decreased GPx, glutathione reductase
Asha Devi et al. 2003[134]	Vitamin E	50 iu/kg	46 m	Rats	12 weeks	5x/wk; 5-30 min/d swimming with a load of 3% body mass tied to tail	60	Time to exhaustion: +33%		
Kim et al. 2017[132]	Vitamin C	500 mg/kg	24 m	Rats	4 weeks	5x/wk; 2 sessions per d swimming for 3 h per session, 45 min rest between sessions	40	No difference in time to exhaustion	No difference in phosphorylation of p38 MAPK and AMPK, or levels of PGC-1a, NRF-1, TFAM	Decreased thiobarbituric acid-reactive substance (TBARS)
Gomez-Cabrera et al. 2008[118]	Vitamin C	500 mg/kg	24 m	Rats	6 weeks	5x/wk; 85 min/d treadmill running at 75% VO2max	30	Time to exhaustion: +27 vs. 187% (*d*= -19.1, [95% CI -26.8, -11.4]) Trend for smaller improvement in VO_{2max}: +4.6 vs. 17.1% (*d*= -0.9, [95% CI -2.1, 0.3])	Reduced expression of NRF-1, TFAM, SOD and GPx	
Higashida et al. 2011[131]	Vitamin C and E	750 mg/kg vit C, 150 mg/g vit E	18 m	Rats	3 weeks	6x/wk; 2 sessions per d swimming for 3 h per session, 45 min rest between sessions	36		No difference in mitochondrial enzymes	Decreased TBARS No difference in SOD1 or SOD2
Meier et al. 2013[129]	Vitamin C, Coenzyme Q10, N-acetylcysteine	140 mg/l vit C, 12mg/l of co-Q10 and 1% NAC	32 m	Mice	4 weeks	5x/wk; 45 min treadmill running	20	No difference in peak power	No difference in CS Decreased expression of SOD1, PGC-1a, or CD36 Increased expression of FABP-3	

Abadi et al. 2013[133]	Vitamin E, Coezyme Q10, alpha lipoic acid	Standard chow with vitamin E (a-tocopherol, 1000 IU), 0.1% a- lipoic acid, and 0.25% CoQ10	36 m, 36 f	Mice	7 weeks	3x/wk; 30-45 min treadmill running	21	No difference in time to exhaustion	No difference in mitochondrial respiratory capacity, CYT-C, PGC-1a	No difference in CAT, SOD1, or SOD2
Strobel et al. 2011[130]	Vitamin E, alpha lipoic acid	1000 iu vit E/kg, 1.6 g/kg ALA	48 m	Rats	14 weeks	4x/wk; 90 min treadmill running at 70% VO2max	56		Decreased PGC-1a mRNA, PGC-1a and COX IV protein, and CS activity	No difference in GPx, xanthine oxidase, or MDA
Wadley et al. 2013[159]	Allopurinol	0.25 mg/ml	24 m	Rats	6 weeks	5x/wk; 20-90 min treadmill running	30		No difference in NRF-2, GLUT4, or SOD mRNA, or PGC-1a, TFAM, CYT-C, CS, and B-HAD	No difference in SOD2
Lee et al. 2015[158]	Epicatechin	1 mg/kg, twice daily	34 m	Mice	8 weeks	5x/wk; 60 min treadmill running at 60% intensity	40	Time to exhaustion: 84 vs. 45% (*d*= 18.0, [95% CI 11.8, 24.3])	Increased CS activity, increased PGC-1B, TFAM	
Dolinsky et al. 2012[195]	Resveratrol	4 g/kg	24 m	Rats	12 weeks	5x/wk; 60 min treadmill running	60	21% longer time to exhaustion (*d*= 1.5, [95% CI 0.5, 2.4])	Increased CS activity, phosphorylation of AMPK, and PGC-1a expression	
Hart et al. 2013[149]	Resveratrol	100 mg/kg	24 m	Rats (bred for high endurance capacity)	12 weeks	5x/wk; 60 min treadmill running	60	VO_{2max}: ~18% increase (*d* = 2.4, [95% CI 0.9, 3.9]), 29% greater running distance during VO_{2max} test	Increased AMPK and SIRT1, decreased PGC-1a	
Hart et al. 2014[150]	Resveratrol	100 mg/kg	24 m	Rats (bred for low endurance capacity)	12 weeks	5x/wk; 60 min treadmill running	60	No difference in VO_{2max}		
Kan et al. 2016[196]	Resveratrol	25 mg/kg	16 m	Mice	4 weeks	7x/wk: 30 min swimming	28	No difference in swim time to exhaustion		
Murase et al. 2005[155]	Green tea extract	0.2-0.5% (wt/wt)	80 m	Mice	10 weeks	2x/wk; 30 min swimming	20	24% longer time to exhaustion (*d*= 2.3, [95% CI 1.2, 3.5])	Increased B-oxidation	
Murase et al. 2006[152]	Green tea extract	0.2-0.5% (wt/wt)	32 m	Mice	8 weeks	3x/wk; 30 min treadmill running	24	30% longer time to exhaustion (*d*= 1.9, [95% CI 0.7, 3.0])	Increased B-oxidation	

HIIT: High-intensity interval training, HR: Heart rate, SIT: sprint-interval training, TTE: Time to exhaustion, PPO: Peak power output, LT: Lactate threshold, RBI: Rest between intervals

Effect size of supplement calculated as Cohen's d when data were available (reported as effect size, 95% CI)

630

631 Table 5: Overview of studies using creatine supplementation during supervised endurance training

	Participants	Training Status	Length	Supplement Dosage	Type of Training	Total Number of Training Sessions	Performance (compared with placebo)
Creatine							
Graef et al. 2009[187]	33 m	Recreationally Active	4 weeks	10 g per day for the first 10 days, then 10 g per day 5x/wk for three weeks (training days only)	Training 5/wk; 3/wk HIIT, 5x2 min at 90-120% PPO, 1 min RBI; 2x/wk recovery, 5x2 min at 80% PPO, 1 min RBI	20	Ventilatory threshold: +16% vs. 10% (*d*= 0.2, [95% CI -0.5, 0.9]) No difference in VO_{2peak}, TTE at VO_{2peak}
Kendall et al. 2009[186]	42 m	Recreationally Active	4 weeks	10 g per day for the first 10 days, then 10 g per day 5x/wk for three weeks (training days only)	Training 5/wk; 3/wk HIIT, 5-6x2 min at 90-120% PPO, 1 min RBI; 2x/wk recovery, 5x2 min at 80% PPO, 1 min RBI	20	Critical power (w): +6.7% vs. no change in control (*d* = 0.1, [95% CI -0.6, 0.8]) No changes in anaerobic working capacity
Forbes et al. 2017[188]	17 f	Recreationally Active	4 weeks	0.3 g/kg body mass/ day for 5 days followed by 0.1 g/kg body mass for 23 days	HIIT 3x/wk; 1 session of 4-6 Wingate tests, 4 min RBI; 1 session of 10-20 6 s sprints, 24 s recovery; 1 session of 8-12x 60 sec at 85% and 60 sec at 15% PPO	12	No difference in VO_{2max}, LT, or time trial performance

HIIT: High-intensity interval training, TTE: Time to exhaustion, PPO: Peak power output, RBI: Rest between intervals
Effect size of supplement calculated as Cohen's d when data were available (reported as effect size, 95% CI)

632

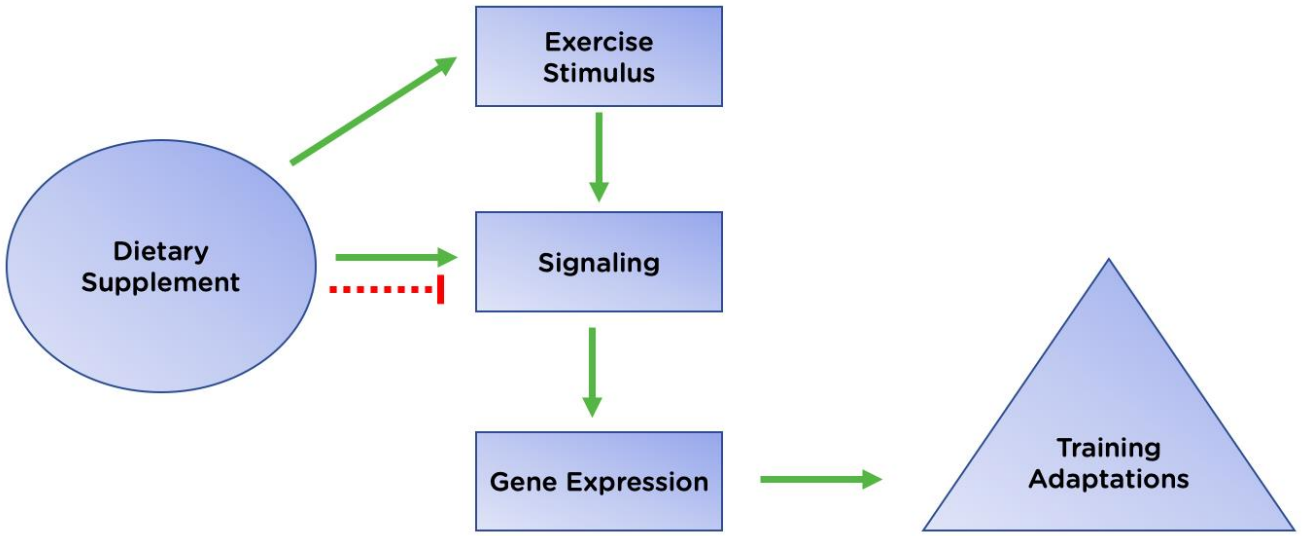

Figure 1. Potential impact of supplements on endurance training adaptations

Green solid line: increases, Red dashed line: inhibits

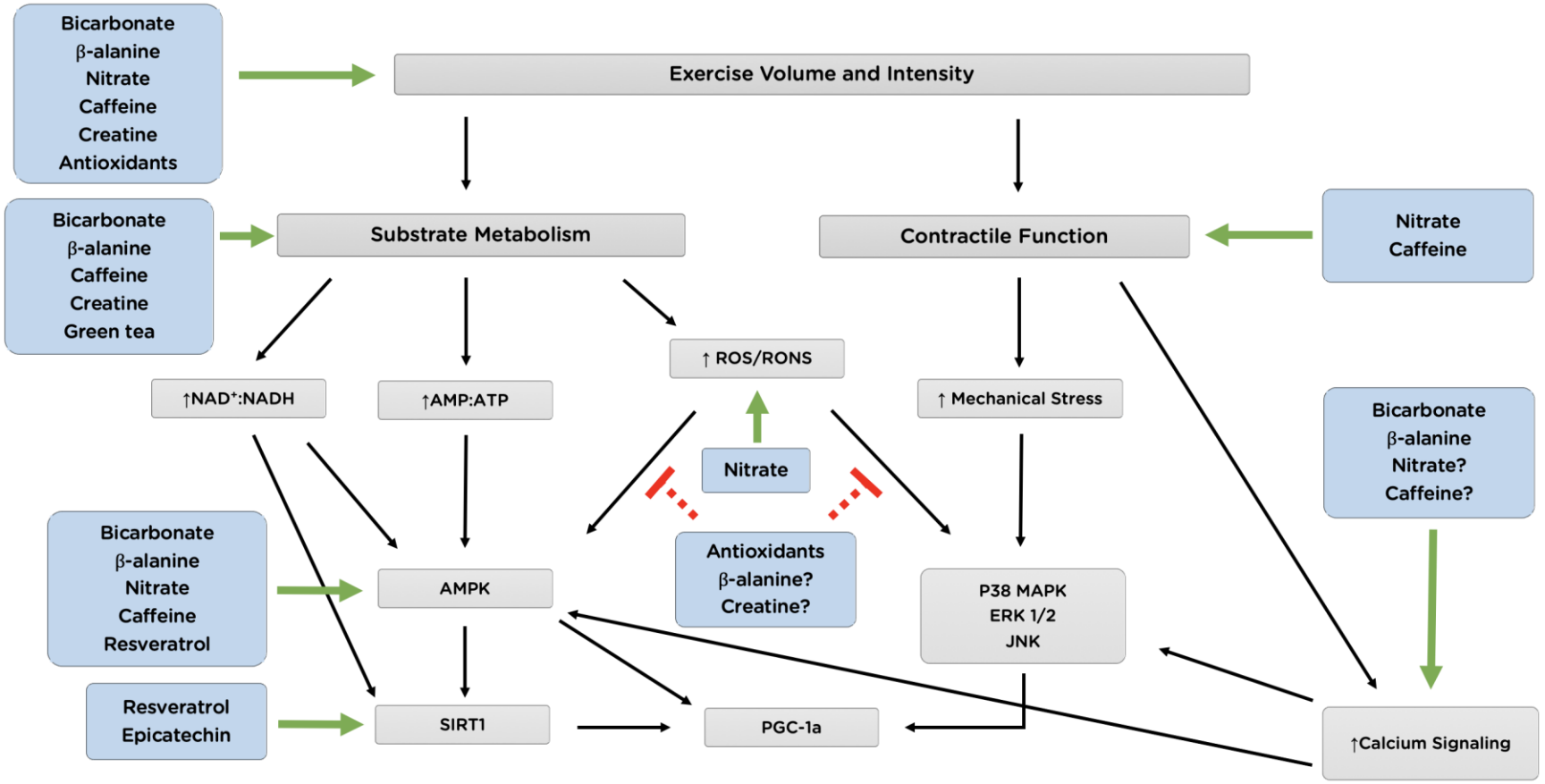

Figure 2. Schematic of areas where dietary supplements have the potential to impact the adaptive responses to endurance training

AMP adenosine monophosphate, AMPK 5' AMP-activated protein kinase, ERK1/2 extracellular-regulated kinase 1 and 2, NADH nicotinamide adenine dinucleotide, p38 MAPK p38 mitogen-activated protein kinase, PGC-1α peroxisome proliferator-activated receptor γ coactivator 1 α, RONS reactive oxygen and nitrogen species, SIRT1 silent mating type information regulation 2 homolog 1. Green solid line: increases, Red dashed line: inhibits. ?= mechanistic potential to occur

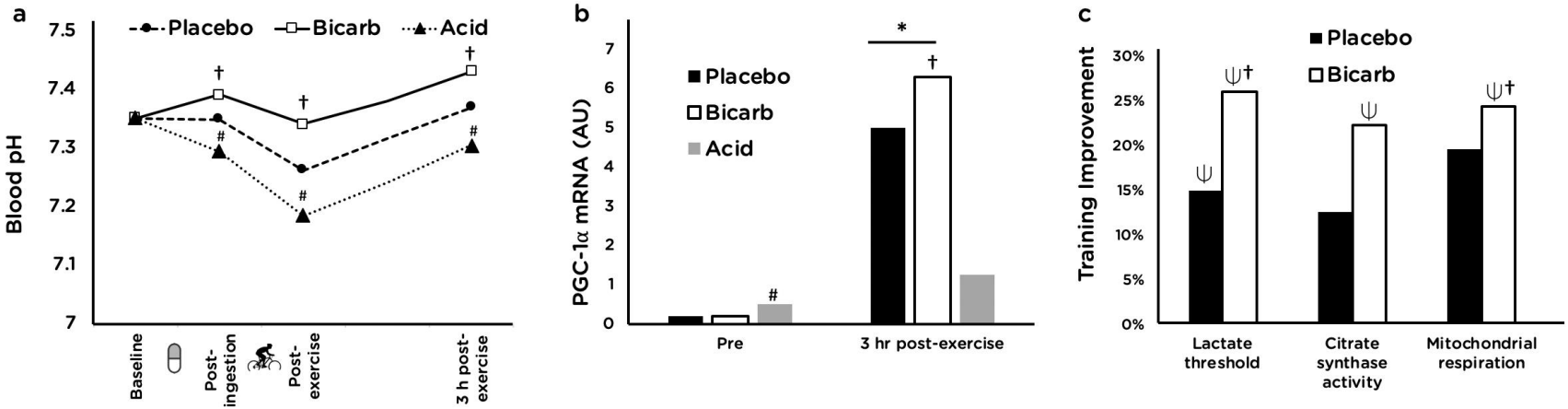

Figure 3. **a** Blood pH responses to high-intensity interval training with ingestion of sodium bicarbonate (Bicarb), ammonium chloride (Acid), or a placebo, **b** effect of pH and training on PGC-1α, and **c** training responses. An alkaline pH can enhance, while a more acidic pH can impair, the acute mRNA response of PGC-1α and longer-term training adaptations to high-intensity interval training. PGC-1α: peroxisome proliferator-activated receptor γ coactivator 1α. *Main effect for time compared with pre-ingestion (P<0.01); †Significant difference from placebo at the time point designated (P<0.01); # Significantly different from placebo and bicarb at the time point designated (p<0.05); ⟂ significant difference from pre-training (p<0.05). Adapted from [22, 27, 33, 35, 37].

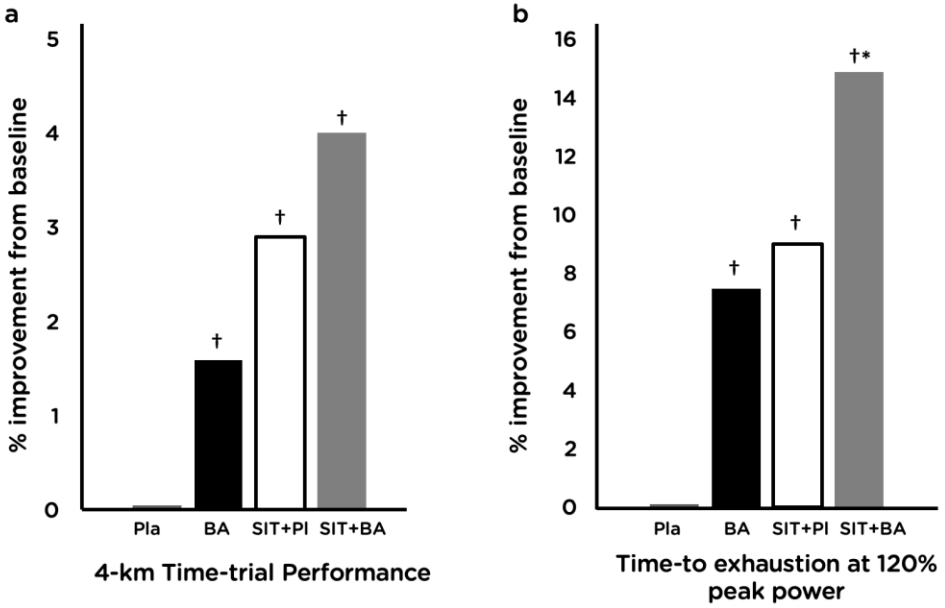

Figure 4. Percent improvement in **a** 4-km time-trial performance and **b** time to exhaustion after 4-wk of placebo and regular training (Pla), 4-wk of beta-alanine supplementation and regular training (BA), 5-wk of sprint-interval training and placebo (SIT+Pla), 4-wk loading phase of beta-alanine followed by 5-wk of sprint-interval training with continued supplementation (SIT+BA), in trained cyclists. Supplementing with β-alanine while maintaining their normal training (BA) reported a 1.6% improvement in 4-km time-trial performance (~6 min) (d = 0.3) and a 7.5% improvement in time-to-exhaustion at 120% of peak power (d = 0.4), compared with no changes in the placebo group, while five weeks of SIT with β-alanine resulted in a greater improvement in time-to-exhaustion (+14.9 vs. 9.0%, d= 0.5) and a trend for greater improvement in time-trial performance compared with a placebo, suggesting both independent and additive benefits of SIT and β-alanine supplementation. †Significant difference from pre-supplementation ($P < 0.05$), *Significant difference from SIT+Pla. Adapted from [53, 60].

Compliance with Ethical Standards

Funding. No sources of funding were used to assist in the preparation of this article.

Conflicts of Interest. Jeffrey Rothschild and David Bishop declare that they have no conflicts of interest relevant to the content of this review.

References

1. Hawley JA. Adaptations of skeletal muscle to prolonged, intense endurance training. Clin Exp Pharmacol Physiol. 2002;29(3):218-22.
2. Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. J Appl Physiol Respir Environ Exerc Physiol. 1984;56(4):831-8. doi:10.1152/jappl.1984.56.4.831.
3. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell metabolism. 2013;17(2):162-84.
4. Perry CG, Lally J, Holloway GP, Heigenhauser GJ, Bonen A, Spriet LL. Repeated transient mRNA bursts precede increases in transcriptional and mitochondrial proteins during training in human skeletal muscle. J Physiol. 2010;588(23):4795-810.
5. Seiler S. What is best practice for training intensity and duration distribution in endurance athletes? Int J Sports Physiol Perform. 2010;5(3):276-91.
6. Rothschild J, Earnest CP. Dietary manipulations concurrent to endurance training. J Funct Morphol Kinesiol. 2018;3(3):41.
7. Knapik JJ, Steelman RA, Hoedebecke SS, Austin KG, Farina EK, Lieberman HR. Prevalence of dietary supplement use by athletes: systematic review and meta-analysis. Sports Med. 2016;46(1):103-23.
8. Lancha Junior AH, Painelli Vde S, Saunders B, Artioli GG. Nutritional strategies to modulate intracellular and extracellular buffering capacity during high-intensity exercise. Sports Med. 2015;45 Suppl 1:S71-81. doi:10.1007/s40279-015-0397-5.
9. Saunders B, Elliott-Sale K, Artioli GG, Swinton PA, Dolan E, Roschel H, et al. beta-alanine supplementation to improve exercise capacity and performance: a systematic review and meta-analysis. Br J Sports Med. 2017;51(8):658-69. doi:10.1136/bjsports-2016-096396.
10. Domínguez R, Cuenca E, Maté-Muñoz JL, García-Fernández P, Serra-Paya N, Estevan MCL, et al. Effects of beetroot juice supplementation on cardiorespiratory endurance in athletes. A systematic review. Nutrients. 2017;9(1):43.
11. Jones AM. Influence of dietary nitrate on the physiological determinants of exercise performance: a critical review. Appl Physiol Nutr Metab. 2014;39(9):1019-28. doi:10.1139/apnm-2014-0036.
12. Peeling P, Binnie MJ, Goods PSR, Sim M, Burke LM. Evidence-based supplements for the enhancement of Aahletic performance. Int J Sport Nutr Exerc Metab. 2018;28(2):178-87. doi:10.1123/ijsnem.2017-0343.
13. Christensen PM, Shirai Y, Ritz C, Nordsborg NB. Caffeine and bicarbonate for speed. A meta-analysis of legal supplements potential for improving intense endurance exercise performance. Front Physiol. 2017;8:240. doi:10.3389/fphys.2017.00240.

14. Nikolaidis MG, Kerksick CM, Lamprecht M, McAnulty SR. Does vitamin C and E supplementation impair the favorable adaptations of regular exercise? Oxid Med Cell Longev. 2012;2012.
15. Gibala MJ, Gillen JB, Percival ME. Physiological and health-related adaptations to low-volume interval training: influences of nutrition and sex. Sports Med. 2014;44 Suppl 2:S127-37. doi:10.1007/s40279-014-0259-6.
16. McNaughton LR, Gough L, Deb S, Bentley D, Sparks SA. Recent developments in the use of sodium bicarbonate as an ergogenic aid. Current sports medicine reports. 2016;15(4):233-44.
17. Hayashi T, Shigetomi T, Ueda M, Kaneda T, Matsumoto T, Tokuno H, et al. Effects of ammonium chloride on membrane currents of acinar cells dispersed from the rat parotid gland. Pflugers Arch. 1992;420(3-4):297-301.
18. Stathopoulou K, Gaitanaki C, Beis I. Extracellular pH changes activate the p38-MAPK signalling pathway in the amphibian heart. J Exp Biol. 2006;209(Pt 7):1344-54. doi:10.1242/jeb.02134.
19. Genders AJ, Martin SD, McGee SL, Bishop DJ. A physiological drop in pH decreases mitochondrial respiration, and AMPK and Akt signalling, in L6 myocytes. bioRxiv. 2018:330662.
20. Balgi AD, Diering GH, Donohue E, Lam KK, Fonseca BD, Zimmerman C, et al. Regulation of mTORC1 signaling by pH. PLoS One. 2011;6(6):e21549. doi:10.1371/journal.pone.0021549.
21. Zhao L, Cui L, Jiang X, Zhang J, Zhu M, Jia J, et al. Extracellular pH regulates autophagy via the AMPK-ULK1 pathway in rat cardiomyocytes. FEBS Lett. 2016;590(18):3202-12. doi:10.1002/1873-3468.12359.
22. Edge, Mundel T, Pilegaard H, Hawke E, Leikis M, Lopez-Villalobos N, et al. Ammonium chloride ingestion attenuates exercise-Induced mRNA levels in human muscle. PLoS One. 2015;10(12):e0141317. doi:10.1371/journal.pone.0141317.
23. Correia-Oliveira CR, Kiss MAPDM. Induced metabolic acidosis by ammonium chloride: action mechanisms, dose and effects on athletic performance. J Phys Educ. 2017;28.
24. Hashimoto T, Hussien R, Oommen S, Gohil K, Brooks GA. Lactate sensitive transcription factor network in L6 cells: activation of MCT1 and mitochondrial biogenesis. The FASEB Journal. 2007;21(10):2602-12. doi:10.1096/fj.07-8174com.
25. Preobrazenski N, Bonafiglia JT, Nelms MW, Lu S, Robins L, LeBlanc C, et al. Does blood lactate predict the chronic adaptive response to training: A comparison of traditional and talk test prescription methods. Applied Physiology, Nutrition, and Metabolism. 2018(ja).
26. Hollidge-Horvat MG, Parolin ML, Wong D, Jones NL, Heigenhauser GJ. Effect of induced metabolic alkalosis on human skeletal muscle metabolism during exercise. Am J Physiol Endocrinol Metab. 2000;278(2):E316-29. doi:10.1152/ajpendo.2000.278.2.E316.
27. Percival ME, Martin BJ, Gillen JB, Skelly LE, MacInnis MJ, Green AE, et al. Sodium bicarbonate ingestion augments the increase in PGC-1α mRNA expression during recovery from intense interval exercise in human skeletal muscle. J Appl Physiol. 2015;119(11):1303-12.
28. Cochran AJ, Percival ME, Tricarico S, Little JP, Cermak N, Gillen JB, et al. Intermittent and continuous high - intensity exercise training induce similar acute but different chronic muscle adaptations. Experimental physiology. 2014;99(5):782-91.

29. Burke LM, Pyne DB. Bicarbonate loading to enhance training and competitive performance. Int J Sports Physiol Perform. 2007;2(1):93-7.
30. Jones RL, Stellingwerff T, Artioli GG, Saunders B, Cooper S, Sale C. Dose-response of sodium bicarbonate ingestion highlights individuality in time course of blood analyte responses. Int J Sport Nutr Exerc Metab. 2016;26(5):445-53. doi:10.1123/ijsnem.2015-0286.
31. Froio de Araujo Dias G, da Eira Silva V, de Salles Painelli V, Sale C, Giannini Artioli G, Gualano B, et al. (In)consistencies in responses to sodium bicarbonate supplementation: a randomised, repeated measures, counterbalanced and double-blind study. PLoS One. 2015;10(11):e0143086. doi:10.1371/journal.pone.0143086.
32. Gough LA, Deb SK, Sparks AS, 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. 2017;47(10):2117-27. doi:10.1007/s40279-017-0699-x.
33. Edge J, Bishop D, 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. 2006;101(3):918-25.
34. Wang J, Qiu J, Yi L, Hou Z, Benardot D, Cao W. Effect of sodium bicarbonate ingestion during 6 weeks of HIIT on anaerobic performance of college students. J Int Soc Sports Nutr. 2019;16(1):18. doi:10.1186/s12970-019-0285-8.
35. Hawke E, Hammarström D, Sahlin K, Tonkonogi M. Does six-weeks of high-intensity cycle training with induced changes in acid-base balance lead to mitochondrial adaptations? J Sci Cycling. 2014;3(2):82.
36. Driller MW, Gregory JR, Williams AD, Fell JW. The effects of chronic sodium bicarbonate ingestion and interval training in highly trained rowers. Int J Sport Nutr Exerc Metab. 2013;23(1):40-7.
37. Bishop DJ, Thomas C, Moore-Morris T, Tonkonogi M, Sahlin K, Mercier J. Sodium bicarbonate ingestion prior to training improves mitochondrial adaptations in rats. Am J Physiol Endocrinol Metab. 2010;299(2):E225-E33.
38. Thomas C, Bishop D, Moore-Morris T, Mercier J. Effects of high-intensity training on MCT1, MCT4, and NBC expressions in rat skeletal muscles: influence of chronic metabolic alkalosis. American Journal of Physiology-Endocrinology and Metabolism. 2007;293(4):E916-E22.
39. Lundby C, Montero D, Joyner M. Biology of VO2max: looking under the physiology lamp. J Acta Physiologica. 2017;220(2):218-28.
40. Stellingwerff T, Anwander H, Egger A, Buehler T, Kreis R, Decombaz J, et al. Effect of two β-alanine dosing protocols on muscle carnosine synthesis and washout. Amino acids. 2012;42(6):2461-72.
41. Stout JR, Cramer JT, Zoeller RF, Torok D, Costa P, Hoffman JR, et al. Effects of beta-alanine supplementation on the onset of neuromuscular fatigue and ventilatory threshold in women. Amino Acids. 2007;32(3):381-6. doi:10.1007/s00726-006-0474-z.
42. Hoffman JR, Ratamess NA, Faigenbaum AD, Ross R, Kang J, Stout JR, et al. Short-duration beta-alanine supplementation increases training volume and reduces subjective feelings of fatigue in college football players. Nutr Res. 2008;28(1):31-5. doi:10.1016/j.nutres.2007.11.004.

43. Baguet A, Koppo K, Pottier A, Derave W. β-Alanine supplementation reduces acidosis but not oxygen uptake response during high-intensity cycling exercise. Eur J Appl Physiol. 2010;108(3):495-503.
44. Gross M, Boesch C, Bolliger CS, Norman B, Gustafsson T, Hoppeler H, et al. Effects of beta-alanine supplementation and interval training on physiological determinants of severe exercise performance. Eur J Appl Physiol. 2014;114(2):221-34. doi:10.1007/s00421-013-2767-8.
45. Glenn J, Gray M, Stewart R, Moyen N, Kavouras S, DiBrezzo R, et al. Incremental effects of 28 days of beta-alanine supplementation on high-intensity cycling performance and blood lactate in masters female cyclists. Amino acids. 2015;47(12):2593-600.
46. Begum G, Cunliffe A, Leveritt M. Physiological role of carnosine in contracting muscle. Int J Sport Nutr Exerc Metab. 2005;15(5):493-514.
47. Boldyrev AA, Aldini G, Derave W. Physiology and pathophysiology of carnosine. Physiol Rev. 2013;93(4):1803-45. doi:10.1152/physrev.00039.2012.
48. Hoetker D, Chung W, Zhang D, Zhao J, Schmidtke VK, Riggs DW, et al. Exercise alters and beta-alanine combined with exercise augments histidyl dipeptide levels and scavenges lipid peroxidation products in human skeletal muscle. J Appl Physiol (1985). 2018. doi:10.1152/japplphysiol.00007.2018.
49. Dutka TL, Lamboley CR, McKenna MJ, Murphy RM, Lamb GD. Effects of carnosine on contractile apparatus Ca2+ sensitivity and sarcoplasmic reticulum Ca2+ release in human skeletal muscle fibers. J Appl Physiol. 2011;112(5):728-36.
50. Hannah R, Stannard RL, Minshull C, Artioli GG, Harris RC, Sale C. β-Alanine supplementation enhances human skeletal muscle relaxation speed but not force production capacity. J Appl Physiol. 2014;118(5):604-12.
51. Turcotte LP, Abbott MJ. Contraction-induced signaling: evidence of convergent cascades in the regulation of muscle fatty acid metabolism. Can J Physiol Pharmacol. 2012;90(11):1419-33. doi:10.1139/y2012-124.
52. Schnuck JK, Sunderland KL, Kuennen MR, Vaughan RA. Characterization of the metabolic effect of β-alanine on markers of oxidative metabolism and mitochondrial biogenesis in skeletal muscle. J Exerc Nutrition Biochem. 2016;20(2):34.
53. Bellinger PM, Minahan CL. Additive benefits of beta-alanine supplementation and sprint-interval training. Med Sci Sports Exerc. 2016;48(12):2417-25. doi:10.1249/MSS.0000000000001050.
54. Walter AA, Smith AE, Kendall KL, Stout JR, Cramer JT. Six weeks of high-intensity interval training with and without β-alanine supplementation for improving cardiovascular fitness in women. J Strength Cond Res. 2010;24(5):1199-207.
55. Cochran AJ, Percival ME, Thompson S, Gillen JB, MacInnis MJ, Potter MA, et al. β-Alanine supplementation does not augment the skeletal muscle adaptive response to 6 weeks of sprint interval training. Int J Sport Nutr Exerc Metab. 2015;25(6):541-9.
56. Wang R, Fukuda DH, Hoffman JR, La Monica MB, Starling TM, Stout JR, et al. Distinct effects of repeated-sprint training in normobaric hypoxia and beta-alanine supplementation. J Am Coll Nutr. 2018:1-13. doi:10.1080/07315724.2018.1475269.
57. Smith AE, Walter AA, Graef JL, Kendall KL, Moon JR, Lockwood CM, et al. 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. 2009;6:5. doi:10.1186/1550-2783-6-5.

58. Santana JO, de Freitas MC, Dos Santos DM, Rossi FE, Lira FS, Rosa-Neto JC, et al. Beta-alanine supplementation improved 10-km running time trial in physically active adults. Front Physiol. 2018;9:1105. doi:10.3389/fphys.2018.01105.
59. Howe ST, Bellinger PM, Driller MW, Shing CM, Fell JW. The effect of beta-alanine supplementation on isokinetic force and cycling performance in highly trained cyclists. Int J Sport Nutr Exerc Metab. 2013;23(6):562-70.
60. Bellinger PM, Minahan CL. Metabolic consequences of β-alanine supplementation during exhaustive supramaximal cycling and 4000-m time-trial performance. Appl Physiol Nutr Metab. 2016;41(8):864-71.
61. Bellinger PM, Howe ST, Shing CM, Fell JW. Effect of combined beta-alanine and sodium bicarbonate supplementation on cycling performance. Med Sci Sports Exerc. 2012;44(8):1545-51. doi:10.1249/MSS.0b013e31824cc08d.
62. Hobson RM, Saunders B, Ball G, Harris R, Sale C. Effects of β-alanine supplementation on exercise performance: a meta-analysis. Amino acids. 2012;43(1):25-37.
63. Church DD, Hoffman JR, Varanoske AN, Wang R, Baker KM, La Monica MB, et al. Comparison of two beta-alanine dosing protocols on muscle carnosine elevations. J Am Coll Nutr. 2017;36(8):608-16. doi:10.1080/07315724.2017.1335250.
64. Saunders B, Sale C, Harris RC, Sunderland C. Sodium bicarbonate and high-intensity-cycling capacity: variability in responses. Int J Sports Physiol Perform. 2014;9(4):627-32. doi:10.1123/ijspp.2013-0295.
65. Naderi A, Earnest CP, Lowery RP, Wilson JM, Willems ME. Co-ingestion of nutritional ergogenic aids and high-intensity exercise performance. Sports Med. 2016;46(10):1407-18. doi:10.1007/s40279-016-0525-x.
66. Painelli VS, Roschel H, Jesus F, Sale C, Harris RC, Solis MY, et al. The ergogenic effect of beta-alanine combined with sodium bicarbonate on high-intensity swimming performance. Appl Physiol Nutr Metab. 2013;38(5):525-32. doi:10.1139/apnm-2012-0286.
67. Danaher J, Gerber T, Wellard RM, Stathis CG. The effect of beta-alanine and NaHCO3 co-ingestion on buffering capacity and exercise performance with high-intensity exercise in healthy males. Eur J Appl Physiol. 2014;114(8):1715-24. doi:10.1007/s00421-014-2895-9.
68. Sale C, Saunders B, Hudson S, Wise JA, Harris RC, Sunderland CD. Effect of beta-alanine plus sodium bicarbonate on high-intensity cycling capacity. Med Sci Sports Exerc. 2011;43(10):1972-8. doi:10.1249/MSS.0b013e3182188501.
69. Lundberg JO, Govoni M. Inorganic nitrate is a possible source for systemic generation of nitric oxide. Free Radical Biology and Medicine. 2004;37(3):395-400.
70. Rimer EG, Peterson LR, Coggan AR, Martin JC, performance. Acute dietary nitrate supplementation increases maximal cycling power in athletes. Int J Sports Physiol Perform. 2016;11(6):715.
71. Larsen FJ, Schiffer TA, Borniquel S, Sahlin K, Ekblom B, Lundberg JO, et al. Dietary inorganic nitrate improves mitochondrial efficiency in humans. Cell Metab. 2011;13(2):149-59. doi:10.1016/j.cmet.2011.01.004.
72. Bailey SJ, Fulford J, Vanhatalo A, Winyard PG, Blackwell JR, DiMenna FJ, et al. Dietary nitrate supplementation enhances muscle contractile efficiency during knee-extensor exercise in humans. J Appl Physiol (1985). 2010;109(1):135-48. doi:10.1152/japplphysiol.00046.2010.

889 73. Hernandez A, Schiffer TA, Ivarsson N, Cheng AJ, Bruton JD, Lundberg JO, et al. Dietary
890 nitrate increases tetanic [Ca2+]i and contractile force in mouse fast-twitch muscle. J
891 Physiol. 2012;590(15):3575-83. doi:10.1113/jphysiol.2012.232777.
892 74. Clementi E, Nisoli E. Nitric oxide and mitochondrial biogenesis: a key to long-term
893 regulation of cellular metabolism. Comp Biochem Physiol A Mol Integr Physiol.
894 2005;142(2):102-10. doi:10.1016/j.cbpb.2005.04.022.
895 75. Thompson C, Wylie LJ, Blackwell JR, Fulford J, Black MI, Kelly J, et al. Influence of dietary
896 nitrate supplementation on physiological and muscle metabolic adaptations to sprint
897 interval training. J Appl Physiol (1985). 2017;122(3):642-52.
898 doi:10.1152/japplphysiol.00909.2016.
899 76. Martins KJ, St-Louis M, Murdoch GK, MacLean IM, McDonald P, Dixon WT, et al. Nitric
900 oxide synthase inhibition prevents activity-induced calcineurin-NFATc1 signalling and fast-
901 to-slow skeletal muscle fibre type conversions. J Physiol. 2012;590(6):1427-42.
902 doi:10.1113/jphysiol.2011.223370.
903 77. De Smet S, Van Thienen R, Deldicque L, James R, Sale C, Bishop DJ, et al. Nitrate intake
904 promotes shift in muscle fiber type composition during sprint interval training in hypoxia.
905 Front Physiol. 2016;7:233. doi:10.3389/fphys.2016.00233.
906 78. Whitfield J, Ludzki A, Heigenhauser GJ, Senden JM, Verdijk LB, van Loon LJ, et al.
907 Beetroot juice supplementation reduces whole body oxygen consumption but does not
908 improve indices of mitochondrial efficiency in human skeletal muscle. J Physiol.
909 2016;594(2):421-35. doi:10.1113/JP270844.
910 79. Egan B, Carson BP, Garcia‐Roves PM, Chibalin AV, Sarsfield FM, Barron N, et al.
911 Exercise intensity‐dependent regulation of peroxisome proliferator‐activated receptor γ
912 coactivator‐1α mRNA abundance is associated with differential activation of upstream
913 signalling kinases in human skeletal muscle. J Physiol. 2010;588(10):1779-90.
914 80. Peeling P, Cox GR, Bullock N, Burke LM. Beetroot juice improves on-water 500 M time-
915 trial performance, and laboratory-based paddling economy in national and international-
916 level kayak athletes. Int J Sport Nutr Exerc Metab. 2015;25(3):278-84.
917 doi:10.1123/ijsnem.2014-0110.
918 81. Croitoru MD, Fülöp I, Fogarasi E, Muntean D-L. Is nitrate a good biomarker of the nitric
919 oxide status?/Este ionul nitrat un bun biomarker al producţiei endogene de monoxid de
920 azot? Rev Rom Med Lab. 2015;23(1):127-35.
921 82. Wylie LJ, Kelly J, Bailey SJ, Blackwell JR, Skiba PF, Winyard PG, et al. Beetroot juice and
922 exercise: pharmacodynamic and dose-response relationships. J Appl Physiol (1985).
923 2013;115(3):325-36. doi:10.1152/japplphysiol.00372.2013.
924 83. Puype J, Ramaekers M, Van Thienen R, Deldicque L, Hespel P. No effect of dietary nitrate
925 supplementation on endurance training in hypoxia. Scand J Med Sci Sports.
926 2015;25(2):234-41.
927 84. Muggeridge DJ, Sculthorpe N, James PE, Easton C. The effects of dietary nitrate
928 supplementation on the adaptations to sprint interval training in previously untrained
929 males. J Sci Med Sport. 2017;20(1):92-7. doi:10.1016/j.jsams.2016.04.014.
930 85. Thompson C, Vanhatalo A, Kadach S, Wylie LJ, Fulford J, Ferguson SK, et al. Discrete
931 physiological effects of beetroot juice and potassium nitrate supplementation following 4-
932 wk sprint interval training. J Appl Physiol. 2018;124(6):1519-28.

933 86. Santana J, Madureira D, de Franca E, Rossi F, Rodrigues B, Fukushima A, et al. Nitrate
934 supplementation combined with a running training program improved time-trial
935 performance in recreationally trained runners. Sports (Basel). 2019;7(5).
936 doi:10.3390/sports7050120.
937 87. Finkel A, Röhrich MA, Maassen N, Lützow M, Blau LS, Hanff E, et al. Long-term effects of
938 NO3- on the relationship between oxygen uptake and power after 3 weeks of
939 supplemented HIHV training. J Appl Physiol. 2018;0(0):null.
940 doi:10.1152/japplphysiol.00176.2018.
941 88. Jonvik KL, Nyakayiru J, Pinckaers PJ, Senden JM, van Loon LJ, Verdijk LB. Nitrate-rich
942 vegetables increase plasma nitrate and nitrite concentrations and lower blood pressure in
943 healthy adults. J Nutr. 2016;146(5):986-93. doi:10.3945/jn.116.229807.
944 89. Wootton-Beard PC, Ryan L. Combined use of multiple methodologies for the
945 measurement of total antioxidant capacity in UK commercially available vegetable juices.
946 Plant Foods Hum Nutr. 2012;67(2):142-7.
947 90. Wylie LJ, Mohr M, Krustrup P, Jackman SR, Ermiotadis G, Kelly J, et al. Dietary nitrate
948 supplementation improves team sport-specific intense intermittent exercise performance.
949 Eur J Appl Physiol. 2013;113(7):1673-84. doi:10.1007/s00421-013-2589-8.
950 91. Bergh U, Thorstensson A, Sjodin B, Hulten B, Piehl K, Karlsson J. Maximal oxygen uptake
951 and muscle fiber types in trained and untrained humans. Med Sci Sports. 1978;10(3):151-4.
952 92. Foster C, Costill DL, Daniels JT, Fink WJ. Skeletal muscle enzyme activity, fiber
953 composition and VO2 max in relation to distance running performance. Eur J Appl Physiol
954 Occup Physiol. 1978;39(2):73-80.
955 93. Sahl RE, Morville T, Kraunsoe R, Dela F, Helge JW, Larsen S. Variation in mitochondrial
956 respiratory capacity and myosin heavy chain composition in repeated muscle biopsies.
957 Anal Biochem. 2018;556:119-24. doi:10.1016/j.ab.2018.06.029.
958 94. Roberts LD, Ashmore T, McNally BD, Murfitt SA, Fernandez BO, Feelisch M, et al.
959 Inorganic nitrate mimics exercise-stimulated muscular fiber-type switching and myokine
960 and γ-aminobutyric acid release. Diabetes. 2017;66(3):674-88.
961 95. Wylie LJ, Ortiz de Zevallos J, Isidore T, Nyman L, Vanhatalo A, Bailey SJ, et al. Dose-
962 dependent effects of dietary nitrate on the oxygen cost of moderate-intensity exercise:
963 Acute vs. chronic supplementation. Nitric Oxide. 2016;57:30-9.
964 doi:10.1016/j.niox.2016.04.004.
965 96. Piknova B, Park JW, Swanson KM, Dey S, Noguchi CT, Schechter AN. Skeletal muscle as
966 an endogenous nitrate reservoir. Nitric Oxide. 2015;47:10-6.
967 97. Coggan AR, Broadstreet SR, Mikhalkova D, Bole I, Leibowitz JL, Kadkhodayan A, et al.
968 Dietary nitrate-induced increases in human muscle power: high versus low responders.
969 Physiol Rep. 2018;6(2). doi:10.14814/phy2.13575.
970 98. Kent GL, Dawson B, Cox GR, Abbiss CR, Smith KJ, Croft KD, et al. Effect of dietary nitrate
971 supplementation on thermoregulatory and cardiovascular responses to submaximal
972 cycling in the heat. Eur J Appl Physiol. 2018;118(3):657-68. doi:10.1007/s00421-018-
973 3809-z.
974 99. Jones AM, Ferguson SK, Bailey SJ, Vanhatalo A, Poole DC. Fiber type-specific effects of
975 dietary nitrate. Exerc Sport Sci Rev. 2016;44(2):53-60.
976 doi:10.1249/JES.0000000000000074.

100. Pingitore A, Lima GP, Mastorci F, Quinones A, Iervasi G, Vassalle C. Exercise and oxidative stress: potential effects of antioxidant dietary strategies in sports. Nutrition. 2015;31(7-8):916-22. doi:10.1016/j.nut.2015.02.005.
101. Moopanar TR, Allen DG. Reactive oxygen species reduce myofibrillar Ca2+ sensitivity in fatiguing mouse skeletal muscle at 37 C. J Physiol. 2005;564(1):189-99.
102. Gomez-Cabrera M-C, Domenech E, Viña J. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. Free Radical Biology and Medicine. 2008;44(2):126-31.
103. Gomez-Cabrera MC, Borras C, Pallardo FV, Sastre J, Ji LL, Vina J. Decreasing xanthine oxidase-mediated oxidative stress prevents useful cellular adaptations to exercise in rats. J Physiol. 2005;567(Pt 1):113-20. doi:10.1113/jphysiol.2004.080564.
104. Irrcher I, Ljubicic V, Hood DA. Interactions between ROS and AMP kinase activity in the regulation of PGC-1α transcription in skeletal muscle cells. American Journal of Physiology-Cell Physiology. 2009;296(1):C116-C23.
105. Merry TL, Ristow M. Do antioxidant supplements interfere with skeletal muscle adaptation to exercise training? J Physiol. 2016;594(18):5135-47.
106. Slattery KM, Dascombe B, Wallace LK, Bentley DJ, Coutts AJ. Effect of N-acetylcysteine on cycling performance after intensified training. Med Sci Sports Exerc. 2014;46(6):1114-23. doi:10.1249/MSS.0000000000000222.
107. McKenna MJ, Medved I, Goodman CA, Brown MJ, Bjorksten AR, Murphy KT, et al. N-acetylcysteine attenuates the decline in muscle Na+,K+-pump activity and delays fatigue during prolonged exercise in humans. J Physiol. 2006;576(Pt 1):279-88. doi:10.1113/jphysiol.2006.115352.
108. Gómez-Cabrera M-C, Pallardó FV, Sastre J, Viña J, García-del-Moral L. Allopurinol and markers of muscle damage among participants in the Tour de France. Jama. 2003;289(19):2503-4.
109. Ichinose T, Nomura S, Someya Y, Akimoto S, Tachiyashiki K, Imaizumi K. Effect of endurance training supplemented with green tea extract on substrate metabolism during exercise in humans. Scand J Med Sci Sports. 2011;21(4):598-605. doi:10.1111/j.1600-0838.2009.01077.x.
110. Borra MT, Smith BC, Denu JM. Mechanism of human SIRT1 activation by resveratrol. J Biol Chem. 2005;280(17):17187-95. doi:10.1074/jbc.M501250200.
111. Gomez-Cabrera MC, Salvador-Pascual A, Cabo H, Ferrando B, Viña J. Redox modulation of mitochondriogenesis in exercise. Does antioxidant supplementation blunt the benefits of exercise training? Free radical biology and medicine. 2015;86:37-46.
112. Tappel A. Vitamin E as the biological lipid antioxidant. Vitamins & Hormones. Elsevier; 1962. p. 493-510.
113. Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee J-H, et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. J Am Coll Nutr. 2003;22(1):18-35.
114. Sharman IM, Down MG, Sen RN. The effects of vitamin E and training on physiological function and athletic performance in adolescent swimmers. Br J Nutr. 1971;26(2):265-76.
115. Lawrence JD, Bower RC, Riehl WP, Smith JL. Effects of alpha-tocopherol acetate on the swimming endurance of trained swimmers. Am J Clin Nutr. 1975;28(3):205-8. doi:10.1093/ajcn/28.3.205.
116. Rokitzki L, Logemann E, Huber G, Keck E, Keul J. alpha-Tocopherol supplementation in racing cyclists during extreme endurance training. Int J Sport Nutr. 1994;4(3):253-64.

117. Oostenbrug G, Mensink R, Hardeman M, De Vries T, Brouns F, Hornstra G. Exercise performance, red blood cell deformability, and lipid peroxidation: effects of fish oil and vitamin E. J Appl Physiol. 1997;83(3):746-52.
118. Gomez-Cabrera MC, Domenech E, Romagnoli M, Arduini A, Borras C, Pallardo FV, et al. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. Am J Clin Nutr. 2008;87(1):142-9. doi:10.1093/ajcn/87.1.142.
119. Braakhuis AJ, Hopkins WG, Lowe TE. Effects of dietary antioxidants on training and performance in female runners. Eur J Sport Sci. 2014;14(2):160-8. doi:10.1080/17461391.2013.785597.
120. Roberts LA, Beattie K, Close GL, Morton JP. Vitamin C consumption does not impair training-induced improvements in exercise performance. Int J Sports Physiol Perform. 2011;6(1):58-69.
121. Bryant RJ, Ryder J, Martino P, Kim J, Craig BW. Effects of vitamin E and C supplementation either alone or in combination on exercise-induced lipid peroxidation in trained cyclists. J Strength Cond Res. 2003;17(4):792-800.
122. Paulsen G, Cumming KT, Holden G, Hallén J, Rønnestad BR, Sveen O, et al. Vitamin C and E supplementation hampers cellular adaptation to endurance training in humans: a double‐blind, randomised, controlled trial. J Physiol. 2014;592(8):1887-901.
123. Yfanti C, Akerström T, Nielsen S, Nielsen AR, Mounier R, Mortensen OH, et al. Antioxidant supplementation does not alter endurance training adaptation. Med Sci Sports Exerc. 2010;42(7):1388-95.
124. Yfanti C, Nielsen AR, Akerstrom T, Nielsen S, Rose AJ, Richter EA, et al. Effect of antioxidant supplementation on insulin sensitivity in response to endurance exercise training. Am J Physiol Endocrinol Metab. 2011;300(5):E761-70. doi:10.1152/ajpendo.00207.2010.
125. Morrison D, Hughes J, Della Gatta PA, Mason S, Lamon S, Russell AP, et al. Vitamin C and E supplementation prevents some of the cellular adaptations to endurance-training in humans. Free Radical Biology and Medicine. 2015;89:852-62.
126. Cumming KT, Raastad T, Holden G, Bastani NE, Schneeberger D, Paronetto MP, et al. Effects of vitamin C and E supplementation on endogenous antioxidant systems and heat shock proteins in response to endurance training. Physiol Rep. 2014;2(10). doi:10.14814/phy2.12142.
127. Ristow M, Zarse K, Oberbach A, Kloting N, Birringer M, Kiehntopf M, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci U S A. 2009;106(21):8665-70. doi:10.1073/pnas.0903485106.
128. Venditti P, Napolitano G, Barone D, Di Meo S. Vitamin E supplementation modifies adaptive responses to training in rat skeletal muscle. Free Radic Res. 2014;48(10):1179-89. doi:10.3109/10715762.2014.937341.
129. Meier P, Renga M, Hoppeler H, Baum O. The impact of antioxidant supplements and endurance exercise on genes of the carbohydrate and lipid metabolism in skeletal muscle of mice. Cell Biochem Funct. 2013;31(1):51-9. doi:10.1002/cbf.2859.
130. Strobel NA, Peake JM, Matsumoto A, Marsh SA, Coombes JS, Wadley GD. Antioxidant supplementation reduces skeletal muscle mitochondrial biogenesis. Med Sci Sports Exerc. 2011;43(6):1017-24. doi:10.1249/MSS.0b013e318203afa3.

131. Higashida K, Kim SH, Higuchi M, Holloszy JO, Han DH. Normal adaptations to exercise despite protection against oxidative stress. Am J Physiol Endocrinol Metab. 2011;301(5):E779-84. doi:10.1152/ajpendo.00655.2010.
132. Kim JC, Park GD, Kim SH. Inhibition of Oxidative Stress by Antioxidant Supplementation Does Not Limit Muscle Mitochondrial Biogenesis or Endurance Capacity in Rats. J Nutr Sci Vitaminol (Tokyo). 2017;63(5):277-83.
133. Abadi A, Crane JD, Ogborn D, Hettinga B, Akhtar M, Stokl A, et al. Supplementation with alpha-lipoic acid, CoQ10, and vitamin E augments running performance and mitochondrial function in female mice. PLoS One. 2013;8(4):e60722. doi:10.1371/journal.pone.0060722.
134. Asha Devi S, Prathima S, Subramanyam MV. Dietary vitamin E and physical exercise: I. Altered endurance capacity and plasma lipid profile in ageing rats. Exp Gerontol. 2003;38(3):285-90.
135. Abbott MJ, Edelman AM, Turcotte LP. CaMKK is an upstream signal of AMP-activated protein kinase in regulation of substrate metabolism in contracting skeletal muscle. Am J Physiol Regul Integr Comp Physiol. 2009;297(6):R1724-R32.
136. Turcotte LP, Raney MA, Todd MK. ERK1/2 inhibition prevents contraction-induced increase in plasma membrane FAT/CD36 content and FA uptake in rodent muscle. Acta Physiol Scand. 2005;184(2):131-9. doi:10.1111/j.1365-201X.2005.01445.x.
137. Nieman DC, Henson DA, McAnulty SR, McAnulty LS, Morrow JD, Ahmed A, et al. Vitamin E and immunity after the Kona Triathlon World Championship. Med Sci Sports Exerc. 2004;36(8):1328-35.
138. Teixeira VH, Valente HF, Casal SI, Marques AF, Moreira PA. Antioxidants do not prevent postexercise peroxidation and may delay muscle recovery. Med Sci Sports Exerc. 2009;41(9):1752-60.
139. Cobley JN, Close GL, Bailey DM, Davison GW. Exercise redox biochemistry: Conceptual, methodological and technical recommendations. Redox Biol. 2017;12:540-8. doi:10.1016/j.redox.2017.03.022.
140. Margaritelis NV, Cobley JN, Paschalis V, Veskoukis AS, Theodorou AA, Kyparos A, et al. Going retro: Oxidative stress biomarkers in modern redox biology. Free Radic Biol Med. 2016;98:2-12. doi:10.1016/j.freeradbiomed.2016.02.005.
141. Forman HJ, Augusto O, Brigelius-Flohe R, Dennery PA, Kalyanaraman B, Ischiropoulos H, et al. Even free radicals should follow some rules: a guide to free radical research terminology and methodology. Free Radic Biol Med. 2015;78:233-5.
142. Somerville V, Bringans C, Braakhuis A. Polyphenols and performance: a systematic review and meta-analysis. Sports Med. 2017;47(8):1589-99. doi:10.1007/s40279-017-0675-5.
143. Kulkarni SS, Canto C. The molecular targets of resveratrol. Biochim Biophys Acta. 2015;1852(6):1114-23. doi:10.1016/j.bbadis.2014.10.005.
144. Jiang Q, Cheng X, Cui Y, Xia Q, Yan X, Zhang M, et al. Resveratrol regulates skeletal muscle fibers switching through the AdipoR1-AMPK-PGC-1α pathway. Food Funct. 2019.
145. Gliemann L, Schmidt JF, Olesen J, Bienso RS, Peronard SL, Grandjean SU, et al. Resveratrol blunts the positive effects of exercise training on cardiovascular health in aged men. J Physiol. 2013;591(20):5047-59. doi:10.1113/jphysiol.2013.258061.
146. Olesen J, Gliemann L, Biensø R, Schmidt J, Hellsten Y, Pilegaard H. Exercise training, but not resveratrol, improves metabolic and inflammatory status in skeletal muscle of aged men. J Physiol. 2014;592(8):1873-86.

147. Scribbans TD, Ma JK, Edgett BA, Vorobej KA, Mitchell AS, Zelt JG, et al. Resveratrol supplementation does not augment performance adaptations or fibre-type–specific responses to high-intensity interval training in humans. Applied Physiology, Nutrition, and Metabolism. 2014;39(11):1305-13.
148. Skrobuk P, von Kraemer S, Semenova MM, Zitting A, Koistinen HA. Acute exposure to resveratrol inhibits AMPK activity in human skeletal muscle cells. Diabetologia. 2012;55(11):3051-60. doi:10.1007/s00125-012-2691-1.
149. Hart N, Sarga L, Csende Z, Koltai E, Koch LG, Britton SL, et al. Resveratrol enhances exercise training responses in rats selectively bred for high running performance. Food Chem Toxicol. 2013;61:53-9. doi:10.1016/j.fct.2013.01.051.
150. Hart N, Sarga L, Csende Z, Koch LG, Britton SL, Davies KJ, et al. Resveratrol attenuates exercise-induced adaptive responses in rats selectively bred for low running performance. Dose Response. 2014;12(1):57-71. doi:10.2203/dose-response.13-010.Radak.
151. Hodgson AB, Randell RK, Jeukendrup AE. The effect of green tea extract on fat oxidation at rest and during exercise: evidence of efficacy and proposed mechanisms. Advances in Nutrition. 2013;4(2):129-40.
152. Murase T, Haramizu S, Shimotoyodome A, Tokimitsu I, Hase T. Green tea extract improves running endurance in mice by stimulating lipid utilization during exercise. Am J Physiol Regul Integr Comp Physiol. 2006;290(6):R1550-6. doi:10.1152/ajpregu.00752.2005.
153. Kuo Y-C, Lin J-C, Bernard JR, Liao Y-H. Green tea extract supplementation does not hamper endurance-training adaptation but improves antioxidant capacity in sedentary men. Applied Physiology, Nutrition, and Metabolism. 2015;40(10):990-6.
154. van Loon LJ, Greenhaff PL, Constantin-Teodosiu D, Saris WH, Wagenmakers AJ. The effects of increasing exercise intensity on muscle fuel utilisation in humans. J Physiol. 2001;536(Pt 1):295-304.
155. Murase T, Haramizu S, Shimotoyodome A, Nagasawa A, Tokimitsu I. Green tea extract improves endurance capacity and increases muscle lipid oxidation in mice. Am J Physiol Regul Integr Comp Physiol. 2005;288(3):R708-15. doi:10.1152/ajpregu.00693.2004.
156. Dong ZX, Wan L, Wang RJ, Shi YQ, Liu GZ, Zheng SJ, et al. (-)-Epicatechin suppresses angiotensin II-induced cardiac hypertrophy via the activation of the SP1/SIRT1 signaling pathway. Cell Physiol Biochem. 2017;41(5):2004-15. doi:10.1159/000475396.
157. Schwarz NA, Blahnik ZJ, Prahadeeswaran S, McKinley-Barnard SK, Holden SL, Waldhelm A. (-)-Epicatechin supplementation inhibits aerobic adaptations to cycling exercise in humans. Front Nutr. 2018;5:132. doi:10.3389/fnut.2018.00132.
158. Lee I, Hüttemann M, Kruger A, Bollig-Fischer A, Malek MH. (–)–Epicatechin combined with 8 weeks of treadmill exercise is associated with increased angiogenic and mitochondrial signaling in mice. Front Pharmacol. 2015;6:43.
159. Wadley GD, Nicolas MA, Hiam D, McConell GK. Xanthine oxidase inhibition attenuates skeletal muscle signaling following acute exercise but does not impair mitochondrial adaptations to endurance training. American Journal of Physiology-Endocrinology and Metabolism. 2013;304(8):E853-E62.
160. Southward K, Rutherfurd-Markwick KJ, Ali A. The effect of acute caffeine ingestion on endurance performance: a systematic review and meta-analysis. Sports Med. 2018. doi:10.1007/s40279-018-0939-8.

161. Lane SC, Areta JL, Bird SR, Coffey VG, Burke LM, Desbrow B, et al. Caffeine ingestion and cycling power output in a low or normal muscle glycogen state. Med Sci Sports Exerc. 2013;45(8):1577-84.
162. Beaumont R, Cordery P, Funnell M, Mears S, James L, Watson P. Chronic ingestion of a low dose of caffeine induces tolerance to the performance benefits of caffeine. J Sports Sci. 2017;35(19):1920-7. doi:10.1080/02640414.2016.1241421.
163. Goncalves LS, Painelli VS, Yamaguchi G, Oliveira LF, Saunders B, da Silva RP, et al. Dispelling the myth that habitual caffeine consumption influences the performance response to acute caffeine supplementation. J Appl Physiol (1985). 2017;123(1):213-20. doi:10.1152/japplphysiol.00260.2017.
164. Graham-Paulson T, Perret C, Goosey-Tolfrey V. Improvements in cycling but not handcycling 10 km time trial performance in habitual caffeine users. Nutrients. 2016;8(7). doi:10.3390/nu8070393.
165. Lara B, Ruiz-Moreno C, Salinero JJ, Del Coso J. Time course of tolerance to the performance benefits of caffeine. PLoS One. 2019;14(1):e0210275. doi:10.1371/journal.pone.0210275.
166. Fredholm BB. Astra Award Lecture. Adenosine, adenosine receptors and the actions of caffeine. Pharmacol Toxicol. 1995;76(2):93-101.
167. Cole KJ, Costill DL, Starling RD, Goodpaster BH, Trappe SW, Fink WJ. Effect of caffeine ingestion on perception of effort and subsequent work production. Int J Sport Nutr. 1996;6(1):14-23.
168. Yeo SE, Jentjens RL, Wallis GA, Jeukendrup AE. Caffeine increases exogenous carbohydrate oxidation during exercise. J Appl Physiol (1985). 2005;99(3):844-50. doi:10.1152/japplphysiol.00170.2005.
169. Van Nieuwenhoven MA, Brummer RM, Brouns F. Gastrointestinal function during exercise: comparison of water, sports drink, and sports drink with caffeine. J Appl Physiol (1985). 2000;89(3):1079-85. doi:10.1152/jappl.2000.89.3.1079.
170. Park S, Scheffler T, Rossie S, Gerrard D. AMPK activity is regulated by calcium-mediated protein phosphatase 2A activity. Cell calcium. 2013;53(3):217-23.
171. Ale-Agha N, Goy C, Jakobs P, Spyridopoulos I, Gonnissen S, Dyballa-Rukes N, et al. CDKN1B/p27 is localized in mitochondria and improves respiration-dependent processes in the cardiovascular system—New mode of action for caffeine. PLoS Biol. 2018;16(6):e2004408.
172. Granata C, Jamnick NA, Bishop DJ. Training-induced changes in mitochondrial content and respiratory function in human skeletal muscle. Sports Med. 2018:1-20.
173. Malek MH, Housh TJ, Coburn JW, Beck TW, Schmidt RJ, Housh DJ, et al. Effects of eight weeks of caffeine supplementation and endurance training on aerobic fitness and body composition. J Strength Cond Res. 2006;20(4):751-5. doi:10.1519/R-18345.1.
174. Vieira JM, Carvalho FB, Gutierres JM, Soares MSP, Oliveira PS, Rubin MA, et al. Caffeine prevents high-intensity exercise-induced increase in enzymatic antioxidant and Na(+)-K(+)-ATPase activities and reduction of anxiolytic like-behaviour in rats. Redox Rep. 2017;22(6):493-500. doi:10.1080/13510002.2017.1322739.
175. Boyett JC, Giersch GE, Womack CJ, Saunders MJ, Hughey CA, Daley HM, et al. Time of day and training status both impact the efficacy of caffeine for short duration cycling performance. Nutrients. 2016;8(10):639.

176. Temple JL, Ziegler AM. Gender differences in subjective and physiological responses to caffeine and the role of steroid hormones. J Caffeine Res. 2011;1(1):41-8. doi:10.1089/jcr.2011.0005.
177. Guest N, Corey P, Vescovi J, El-Sohemy A. Caffeine, CYP1A2 genotype, and endurance performance in athletes. Med Sci Sports Exerc. 2018. doi:10.1249/MSS.0000000000001596.
178. Spriet LL. Exercise and sport performance with low doses of caffeine. Sports Med. 2014;44 Suppl 2:S175-84. doi:10.1007/s40279-014-0257-8.
179. Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, et al. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr. 2017;14:18. doi:10.1186/s12970-017-0173-z.
180. Harris RC, Soderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci (Lond). 1992;83(3):367-74.
181. Green AL, Hultman E, Macdonald IA, Sewell DA, Greenhaff PL. Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am J Physiol. 1996;271(5 Pt 1):E821-6. doi:10.1152/ajpendo.1996.271.5.E821.
182. Wallimann T, Tokarska-Schlattner M, Schlattner U. The creatine kinase system and pleiotropic effects of creatine. Amino Acids. 2011;40(5):1271-96. doi:10.1007/s00726-011-0877-3.
183. Kuznetsov AV, Tiivel T, Sikk P, Kaambre T, Kay L, Daneshrad Z, et al. Striking differences between the kinetics of regulation of respiration by ADP in slow‐twitch and fast‐twitch muscles in vivo. European journal of biochemistry. 1996;241(3):909-15.
184. Rahimi R. Creatine supplementation decreases oxidative DNA damage and lipid peroxidation induced by a single bout of resistance exercise. J Strength Cond Res. 2011;25(12):3448-55. doi:10.1519/JSC.0b013e3182162f2b.
185. Tomcik KA, Camera DM, Bone JL, Ross ML, Jeacocke NA, Tachtsis B, et al. Effects of creatine and carbohydrate loading on cycling time trial performance. Med Sci Sports Exerc. 2018;50(1):141-50. doi:10.1249/MSS.0000000000001401.
186. Kendall KL, Smith AE, Graef JL, Fukuda DH, Moon JR, Beck TW, et al. Effects of four weeks of high-intensity interval training and creatine supplementation on critical power and anaerobic working capacity in college-aged men. J Strength Cond Res. 2009;23(6):1663-9. doi:10.1519/JSC.0b013e3181b1fd1f.
187. Graef JL, Smith AE, Kendall KL, Fukuda DH, Moon JR, Beck TW, et al. The effects of four weeks of creatine supplementation and high-intensity interval training on cardiorespiratory fitness: a randomized controlled trial. J Int Soc Sports Nutr. 2009;6:18. doi:10.1186/1550-2783-6-18.
188. Forbes SC, Sletten N, Durrer C, Myette-Côté É, Candow D, Little JP. Creatine Monohydrate supplementation does not augment fitness, performance, or body composition adaptations in response to four weeks of high-intensity interval training in young females. Int J Sport Nutr Exerc Metab. 2017;27(3):285-92.
189. McCracken M, Ainsworth B, Hackney AC. Effects of the menstrual cycle phase on the blood lactate responses to exercise. Eur J Appl Physiol Occup Physiol. 1994;69(2):174-5.

190. Chwalbinska-Moneta J. Effect of creatine supplementation on aerobic performance and anaerobic capacity in elite rowers in the course of endurance training. Int J Sport Nutr Exerc Metab. 2003;13(2):173-83.
191. Nelson AG, Day R, Glickman-Weiss EL, Hegsted M, Kokkonen J, Sampson B. Creatine supplementation alters the response to a graded cycle ergometer test. Eur J Appl Physiol. 2000;83(1):89-94. doi:10.1007/s004210000244.
192. Maughan RJ. Contamination of dietary supplements and positive drug tests in sport. J Sports Sci. 2005;23(9):883-9. doi:10.1080/02640410400023258.
193. Shill DD, Southern WM, Willingham TB, Lansford KA, McCully KK, Jenkins NT. Mitochondria‐specific antioxidant supplementation does not influence endurance exercise training‐induced adaptations in circulating angiogenic cells, skeletal muscle oxidative capacity or maximal oxygen uptake. J Physiol. 2016;594(23):7005-14.
194. Polley KR, Jenkins N, O'Connor P, McCully K. Influence of exercise training with resveratrol supplementation on skeletal muscle mitochondrial capacity. Appl Physiol Nutr Metab. 2016;41(1):26-32. doi:10.1139/apnm-2015-0370.
195. Dolinsky VW, Jones KE, Sidhu RS, Haykowsky M, Czubryt MP, Gordon T, et al. Improvements in skeletal muscle strength and cardiac function induced by resveratrol during exercise training contribute to enhanced exercise performance in rats. J Physiol. 2012;590(11):2783-99. doi:10.1113/jphysiol.2012.230490.
196. Kan NW, Ho CS, Chiu YS, Huang WC, Chen PY, Tung YT, et al. Effects of resveratrol supplementation and exercise training on exercise performance in middle-aged mice. Molecules. 2016;21(5). doi:10.3390/molecules21050661.