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A Systematic Risk Assessment and Meta-Analysis on the Use of Oral Beta-Alanine Supplementation

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Supplementary File 2: Evidence from human longitudinal studies

Supplementary File 3: Evidence from human acute studies

Supplementary File 4: Evidence from animal studies

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ABSTRACT: β-alanine (BA) supplementation is one of the world's most commonly used sports supplements, and its use as a nutritional strategy in other populations is ever-increasing, due to evidence of pleiotropic ergogenic and therapeutic benefits. Despite its wide-spread use, limited understanding of potential adverse effects is available. In order to address this, a systematic risk assessment and meta-analysis, based on PRISMA guidelines, was undertaken. Four databases were searched using keywords and MESH headings. All human and animal studies that investigated an isolated, oral, BA supplementation strategy were included. Data were extracted according to 5 main outcomes, including: 1) Side-effects reported during longitudinal trials, 2) Side-effects reported during acute trials, 3) Effect of supplementation on health-related biomarkers, 4) Effect of supplementation on related elements (taurine and histidine), 5) Outcomes from animal trials. Quality of evidence for outcomes were ascertained using GRADE recommendations and all quantitative data were meta-analysed using multi-level models grounded in Bayesian principles. 101 human and 50 animal studies were included. Paraesthesia was the only reported side-effect and had an estimated odds ratio of 8.9 (95%CrI: 2.2, 32.6) with supplementation relative to placebo. Participants in active treatment groups experienced similar drop-out rates to those receiving the placebo treatment [Odds ratio: 0.72 (95%Crl: 0.50, 1.05)]. BA supplementation caused a small increase in ALT content (ES: 0.274, Crl: 0.04, 0.527) although mean data remained well within clinical reference ranges. Meta-analysis of human data showed no main effect of BA supplementation on taurine (ES; 0.002; 95%Crl: -0.48, 0.47) or histidine (-0.15; 95%Crl: -0.64, 0.33). A main effect of BA supplementation on taurine content was reported for murine models, but only when the daily dose was ≥3% BA in drinking water. Intervention duration did not moderate this effect. The results of this review indicate that BA supplementation within the doses used in research designs, does not adversely affect those consuming it.

KEYWORDS: Carnosine; taurine; histidine; paraesthesia; safety; adverse effects.

INTRODUCTION

The primary role of carnosine (β-alanine-L-histidine) in skeletal muscle metabolism is to act as an intracellular buffer (1), with additional potential actions including the reduction of reactive oxygen/nitrogen species, and/or calcium regulation (2,3). β-alanine (BA) availability is the limiting step in intra-muscular carnosine (MCarn) synthesis. Accordingly, supplementation increases MCarn content (4,5), the ergogenic potential of which is well established. A recent meta-analysis confirmed the efficacy of BA supplementation to improve high-intensity exercise performance, with optimum benefit reported for capacity based assessments lasting between 30 seconds and 10 minutes (6). Accordingly, BA is one of just five sports supplements recognised by the International Olympic Committee as having sufficient evidence of efficacy to warrant its use in specific situations (7). Additionally, therapeutic supplementation with BA is gaining in popularity. Recently, the therapeutic potential of carnosine was reviewed (8) and a wide range of targets and conditions that may be improved by BA or carnosine supplementation were highlighted. These included protection against the effects of senescence (9), conveying a neuro-protective influence (10,11), inhibition of tumour growth (12), improved clinical outcomes in participants suffering from Parkinson's disease (13), enhanced glucose sensitivity (14) and accelerated recovery following acute kidney failure (15). Much of this evidence was based on animal or *in-vitro* models, and the efficacy of BA supplementation to meaningfully impact these parameters in clinical trials has yet to be ascertained. The therapeutic potential of BA supplementation represents a topical and exciting progression of the current evidence base, and research in this area is likely to exponentially increase in the coming years, as ever-more targets are identified for this pleiotropic nutritional agent.

In contrast to a large and increasing evidence base for ergogenic and therapeutic effects of BA supplementation, limited information is available on the safety of this nutritional strategy.

Regular risk assessment of common nutritional supplements and ergogenic aids is essential as nutrients generally exert a biphasic dose response, whereby optimal intakes exert a stimulatory and beneficial response, while lower or higher intakes may be harmful or inhibitory. Theoretical concerns related to an excess intake of beta-alanine include a possible reduction of taurine and/or free histidine content. Reduced intra-cellular taurine may occur as elevated BA availability increases competition for their shared transporter, *Tau-T* (16). Histidine is also required for carnosine synthesis, and if not matched by dietary intake, the free histidine pool may become depleted as a result of chronic BA supplementation (17). Additionally, BA supplementation has been reported to cause acute paraesthesia, which has been described as an uncomfortable sensation on the surface of the skin that occurs within 10 – 20 minutes following ingestion (4). Little is known about the occurrence or physiological consequences of these outcomes. The aim of the current investigation, therefore, was to undertake a systematic risk assessment of BA supplementation, comprising comprehensive review and analysis procedures, to synthesise and evaluate all available evidence from both human and animal trials.

METHODS

This risk assessment followed recommendations from the Council for Responsible Nutrition (CRN) Vitamin and Mineral Safety, 3rd Edition (18), which are commonly used to risk assess nutritional supplements (19,20). The protocol was designed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (21). The review was prospectively registered in an international register of systematic reviews (PROSPERO registration no. CRD42017071843).

Study Selection:

Study selection was guided by the PICOS (population, intervention, comparator, outcomes and study design) approach, and the criteria within each of these categories were as follows:

- ***Population:*** Human populations were restricted to healthy individuals of any age or activity level. Animal models were considered for inclusion only if conducted on healthy, wild-type mammals.
- ***Intervention:*** Original studies investigating the effects of isolated oral BA supplementation interventions were considered for inclusion in the review.
- ***Comparator:*** No human comparators were required, but randomised, blinded, placebo-controlled studies were assigned a higher quality rating and prioritised in the interpretation of results.
- ***Outcomes:*** Human data were analysed according to 4 outcomes, namely 1) side-effects reported during longitudinal trials, 2) side-effects reported during acute trials, 3) effect of supplementation on health-related biomarkers and 4) effect of supplementation on related compounds. For the animal trials, data related to species, dosing strategy, study aims and primary outcomes were extracted. Dosing strategy was reported as intervention length (days), the concentration of BA provided in the drinking water (%) or chow, and the total dose ingested by each animal ($mgBA \cdot gBW^{-1}$). Daily intake ($g \cdot day^{-1}$) was based on the mean weight of the animals in the BA group, estimated as the mean of the start and end weights reported. If not reported, weights were estimated using normative data from the same strain (http://www.arc.wa.gov.au/?page_id=125). If specific fluid intakes were not reported, these were estimated assuming an intake of $0.1ml \cdot g^{-1}$ for rats, and $0.15ml \cdot g^{-1}$ for mice ().

- ***Study Design:*** Only studies that used an intervention-based study design were included within the review.

Search Strategy

A three-stage screening strategy (title/abstract screening; full-text screen; full text appraisal) was independently undertaken by two reviewers. The search was conducted using 4 databases (Medline; Embase; Sport Discus and Web of Science) with the terms "beta alanine" OR "carnosine" concatenated with "intervention" OR "trial" OR "supplementation" OR "health" OR "safety" OR "paraesthesia" OR "taurine" OR "side-effect" OR "adverse effect" OR "toxicity". In addition, MESH heading searches, with the key-term beta-alanine were conducted using Medline and Embase, and with database specific subheadings. Searches were limited to original studies in English published between 1980 and 2018. The final searches were completed in September 2018.

Quality Appraisal and Data Extraction

All data were extracted using a pre-piloted spreadsheet, and independently verified by a second member of the review team. Quality ratings for outcomes 1 and 2 (side-effects reported in all acute and longitudinal human trials) were assigned using the recommendations of the GRADE working group (Grading of Recommendations Assessment Development and Evaluation) (22). An *a-priori* ranking of high, moderate or low was assigned, based on whether the study was a randomised placebo-controlled trial, a non-randomised placebo controlled trial or a non-randomised and non-placebo-controlled intervention trial. Studies were also provided an *a-priori* ranking of high quality if they used a matched pair allocation design. Studies were then assessed, and down-graded a level if appropriate, based on the response to 3 questions, *i.e.* 1) were participants blinded to the treatment? 2) were side-effects reported in the study? 3) were participants specifically instructed to report side-effects? This procedure allowed the quality of

evidence for each outcome to be categorised as “high”, “moderate”, “low” or “very low”, with the cumulative outcome score based on the median score assigned.

Data Analysis

All meta-analyses were conducted within a Bayesian framework enabling studies with zero events to be included without requiring correction factors. In addition, Bayesian methods enabled log odds ratios to be modelled without assuming a normal distribution and provided an efficient means of down-weighting potentially biased studies, *i.e.*, those without a control condition (23). Hierarchical Bayesian random effects models were used to meta-analyse outcome data on cases reporting paraesthesia and drop outs. Binomial specifications were used at the first level of the model to estimate probability of an event, with parameters allowed to vary across studies. Intercept terms for logit transformed probabilities were estimated for the control comparison and an additional effect term included for active supplementation. Effect terms were assumed to follow a normal distribution at the second level of the hierarchical model, with the mean representing the average log odds ratio across all studies and the variance indicating study-to-study variability. Non-informative normal and uniform priors were used for the mean and variance parameters, respectively.

The effects of BA supplementation on tissue taurine and histidine content in human and animal populations were quantified using standardized mean difference effect sizes. Standard formulae for raw score effect sizes and associated sampling variances were used for independent-groups post-test (animal studies only), single-group pretest-posttest (24) and pretest-posttest-control study designs (25). Observed effect sizes were assumed to follow a normal distribution with mean identified by hyper-parameters representing the average effect across all studies and variance indicating study-to-study variability. To control for potential bias in human studies featuring non-controlled designs, a sensitivity analysis comprising down-

weighting of effect sizes through a hierarchical power prior model was included (26). Finally, a meta-regression controlling for daily dose (less than, or equal to, 3%) and total cumulative dose ($mgBA{\cdot}gBW^{-1}$) was included for animal studies measuring taurine levels post-supplementation. Inferences from all Bayesian models were performed on posterior samples generated by Markov Chain Monte Carlo with 95% credible intervals (CrIs) constructed. Models were run in OpenBUGS (version 3.2.3, MRC Biostatistics Unit, Cambridge UK) and in R (version 3.3.1 R Development Core Team) using the R2OpenBugs package (https://CRAN.R-project.org/package=rbugs).

RESULTS

Study Characteristics

One hundred and one human intervention studies (94 longitudinal and 8 acute, with one study comprising both acute and longitudinal arms; (4)), and 50 animal studies were included in the review (see Figure 1). In total 2,268 humans were included in the final analyses (1,820 men and 448 women), with 1,295 of these consuming the active BA supplement. The majority of studies were conducted on healthy young adults, and participants had a median (IQR) age of 23.5 (5.5) yrs. Seven studies were conducted using a population with a mean age > 50 yrs (9,27–32) and 5 studies were conducted using adolescent populations (mean age: 10 - 19 years (33–37). The majority of longitudinal studies were conducted using athletic groups (48%), or recreationally trained (34%) populations, with the remaining described as being untrained (8%), or undefined (10%). Further information related to the training type and status of participants is provided in Supplementary Files 1 and 2 (SF 1 & 2). Three inclusions within the review were based on data sourced outside of the described search-strategy. Two of these were presented at international conferences (38,39) and the other was a doctoral thesis, (40). The

decision to include these datasets was based on their relevance to the topic area, along with the completeness of data and design information available.

Outcome 1: Side-effects reported during longitudinal trials

Ninety-four longitudinal studies, comprising 99 outcomes, were identified, and are described in Supplementary File 1. The median (IQR: range) intervention period and daily dose was 28 (14: 7-168) days, and 6 (1.65: 1.6-12) $g \cdot day^{-1}$, resulting in a total cumulative dose of 179.2 (60.5: 34.3-1075.2) g. The quality of evidence for side-effects reported was primarily moderate or low (23% high; 34% moderate; 33% low; 9% very low; Figure 2 Panel A). Ninety-one percent of studies were initially allocated an *a-priori* rating of "high quality", but most were subsequently downgraded based on the secondary nature of side-effect reporting, which resulted in the provision of limited information regarding side-effects experienced and the mode of assessment. Meta-analysis of withdrawal rates between participants allocated to BA or placebo groups were non-significant (Odds ratio: 0.72; 95%CrI: 0.50, 1.05). Two additional sensitivity analyses were conducted after: 1) removing data from studies that reported very high withdrawal rates from both groups (28,41) (Odds ratio: 0.67; 95%CrI: 0.39 – 1.01) and 2) including data only from studies that specifically reported withdrawal information (Odds ratio: 0.74; 95%CrI: 0.45 – 1.05). These sensitivity analyses did not alter the original findings. Analysis of incidence of paraesthesia was conducted with data from studies that were assigned a "high" quality rating only (n = 22, with 285 and 219 participants assigned to the BA and PLA groups respectively). Incidence of paraesthesia was 18.6% in the active treatment group and 5.7% in the placebo group. Meta-analysis of reported incidences of paraesthesia demonstrated a significantly increased likelihood of paraesthesia reporting with active supplementation (Odds ratio: 8.9; 95%CrI: 2.2 – 32.6). Wide variation in both the incidence and severity of paraesthesia symptoms were evident. This finding, along with wide heterogeneity in study design, dosing protocols, compliance monitoring and mode of side-effect reporting precluded

statistical identification of factors that moderated paraesthesia. One longitudinal study examined paraesthesia occurrence when participants were provided a fixed dose of 6g·day^{-1} of BA for 28 days, in either sustained or rapid release formulations (42). The group who ingested the rapid release formulation reported a more frequent paraesthesia occurrence than those who consumed the sustained release formulation. This group reported a similar paraesthesia occurrence to the placebo group. No differences in compliance were identified between the groups.

Outcome 2: Side-effects reported during acute trials

Eight studies, comprising nine outcomes, reported data related to side-effects experienced during acute BA supplementation were identified (4,40,43–49), and are described in Supplementary File 2. The median (IQR: range) dose ingested was 1.6 (0.38: 0.8-3.2) g and the quality of evidence for this outcome measure was primarily "high" (56% high, 22% moderate, 22% low, Figure 2 Panel B). Statistical meta-analyses of outcomes were not conducted due to the small number of studies available, combined with large heterogeneity in study design and outcome measures, and so a narrative synthesis is presented. Similar to longitudinal trials, paraesthesia was the only side-effect reported. The extent and time to peak blood BA concentration emerged as the primary determinant of the occurrence and intensity of paraesthesia. This was first investigated by Harris et al. (2006), who administered different acute BA forms and doses. BA (40mg·kgBM^{-1}) ingested in the form of carnosine and anserine contained in chicken broth did not result in paraesthesia, while an equivalent intake of BA in its pure form invoked responses of tingling, itch and irritation, representative of paraesthesia (4). Response occurred in a dose related manner with 40mg·kgBM^{-1} (~3.2g) causing sensations that were considered unpleasant by all participants, and intolerable by 2. In contrast, lower doses (10 and 20 mg·kgBM^{-1}/~0.8 and 1.6g) invoked similar sensations, but of milder intensities. Decombaz et al. (2012), investigated response to an equivalent BA intake (1.6g),

provided in slow-release capsules or in its pure form dissolved in aqueous solution. Participants completed questionnaires related to paraesthesia symptoms in parallel with blood sampling. Only BA in solution produced evident sensations, with the intensity described as "pins and needles". Sensory response anticipated and paralleled that of plasma BA concentration, and paraesthesia symptoms were influenced by the extent and time to peak plasma BA concentration (44). Stautemas et al. (2018) investigated the influence of acute ingestion of a fixed (1.4g) vs a weight relative (10mg·kgBW^{-1}) dose on BA pharmacokinetics. Paraesthesia was not reported by any participant consuming the weight-relative dose, while 2 of the 28 participants experienced paraesthesia in the fixed dose group, the timing of which matched their individual Cmax. Some evidence exists suggesting that ethnicity, sex (46) or the individual's body size (40) may moderate the occurrence, or intensity, of paraesthesia experienced. More specifically, Asians, women and lighter individuals (<75) reported stronger or more frequent experience of paraesthesia compared to Caucasians, men and men heavier than 85kg.

Outcome 3: Effect of BA supplementation on health-related biomarkers

Seven studies reported data on the influence of BA supplementation on circulating health-related biomarkers (4,9,28,39,50–52), comprising 220 individuals, with 87 of these taking the active BA supplement. These studies used a median (IQR) total cumulative dose of 179.2 (84)g. Studies were conducted using older male and female participants (9,28), healthy young males (4,39,50), healthy young men and women (51) or trained cyclists (52). No individual study reported a significant change to any of the measured biomarkers. Meta-analyses were conducted on any marker that was measured in 2 or more studies and results are presented in Table 1. A statistically significant effect of BA supplementation was obtained for alanine aminotransferase (ES: 0.274; 95%CrI: 0.04, 0.527), while trends toward significantly increased alkaline phosphatase (ES: 0.434; 95%CrI: -0.067, 0.811) and sodium (ES: 0.497; 95%CrI: -

0.033, 1.063) were also observed. Additionally, Harris et al. (2006) conducted a 12-lead ECG, and reported no change to cardiac function following a 4 week BA supplementation intervention (4).

Outcome 4: Effect of BA supplementation on taurine and histidine (human data)

Five studies reported data on the effect of BA supplementation on taurine (4,17,38,39,53) and four on histidine (17,42,51,54). Taurine content was measured in 63 individuals with 45 allocated to the active BA supplement, while histidine content was measured in 73 individuals with 55 allocated to the active BA supplement. Meta-analyses indicated that, in humans, the BA supplementation protocols employed did not exert an effect on skeletal muscle taurine (ES: 0.002; 95%CrI: -0.48, 0.47, Figure 3) or histidine (ES: -0.15; 95%CrI: -0.64, 0.33). Sensitivity analyses conducted to control for potential bias in studies not including a placebo comparative group did not meaningfully change results attained for any of these parameters (data not shown).

Outcome 5: Outcomes from animal studies

Fifty animal studies were included in the review, and an overview of these studies is provided in Supplementary File 3. Meta-analyses of all studies including data on tissue taurine content in both BA supplemented and pair-fed control murines indicated a main effect of BA supplementation on taurine content (ES: -1.94; 95%CrI: -2.39, -1.52). Substantial variation existed in relation to the potential effect of moderators including daily dose, intervention duration, total cumulative dose and tissue type. Following a sequential modelling approach to account for potential moderators and reduce between-study heterogeneity, a final meta-regression was performed using data from cardiac or skeletal muscle only, and included a binary variable (daily dose: <3% or ≥3% of BA in drinking water), and a covariate (Total cumulative dose (TCD) $mgBA \cdot gBW^{-1}$). No effect of BA supplementation on taurine content

was shown when a daily dose of <3% was ingested (ES: -0.32, 95%CrI: -0.80, 0.14, Figure 4), while a dose of 3% induced a significant reduction to tissue taurine content (ES: -2.71, 95%CrI: -3.33, -2.15, Figure 5). The difference between these doses was statistically significant (ES: -2.35; 95%CrI: -3.27, -1.48). No effect of TCD (ES: -0.007; 95%CrI: -0.030, 0.017) was obtained, nor an interaction between daily dose and TCD (ED: 0.021; 95%CrI: -0.010, 0.051). Only one study reported data on the effect of BA supplementation on tissue histidine content (55). This study provided data on histidine content in 5 brain sites, and no effect of BA supplementation was identified (ES: 0.57; 95%CrI: -0.24, 1.39).

DISCUSSION

No adverse effects of oral beta-alanine supplementation, within the doses and intervention durations investigated, were identified within this systematic risk assessment. Meta-analysis of animal data indicates that BA supplementation of at least 3% is required to reduce cardiac or skeletal muscle tissue taurine content, and that this reduction is not impacted by intervention duration. Meta-analysis of human data showed no effect of BA supplementation on muscle taurine or histidine content, likely due to the lower relative doses employed in human studies. Paraesthesia was the only side-effect identified during human trials, however no evidence exists to indicate that this is harmful, and thus it is not considered to represent an adverse event. Participants in the active treatment groups were not found to experience higher drop-out rates than those consuming a placebo. Although a significant effect of BA supplementation on ALT content was identified, the effect was small, and supplementation did not meaningfully alter any of the other health-related biomarkers reported.

Effect of BA supplementation on health-related biomarkers

A wide range of clinical biomarkers were investigated pre and post-supplementation, including indicators of renal, muscle and hepatic function, along with various clinical haematological markers. No individual study reported a significant effect of BA supplementation on any of these biomarkers (4,9,28,39,50,51). Additionally, two studies conducted additional analyses, to identify the proportion of individuals with values outside of normative ranges for each of the biomarkers identified, and whether this varied between the BA and PLA group (39,50). No trends were apparent from either of these studies. Meta-analysis of any biomarker that was measured in two or more studies, did however, show a main effect of BA supplementation on ALT content, along with trends toward an increase in sodium and alkaline phosphatase (ALP). ALT is a transaminase enzyme, which is primarily present in the liver. Liver damage may cause ALT to "leak" into the bloodstream, and thus elevated blood levels can be indicative of liver dysfunction. Statistical meta-analysis indicated a "small" effect of BA supplementation on blood ALT content (ES: 0.274; CrI: 0.04, 0.527). Considering the pooled SD of all baseline data reported (11.7), this would correspond to a mean increase of ~3.2 $U{\cdot}L^{-1}$ for each participant within the BA groups. Considering that mean baseline ALT content was 22.5 $U{\cdot}L^{-1}$, this small increase would still result in blood ALT levels well within clinical reference ranges, which are typically considered to be <40-55 $U{\cdot}L^{-1}$, although wide variation in individual lab reference ranges do exist. Interestingly, it has previously been reported that only a small amount of supplemented beta-alanine (~3%) is actually used for carnosine synthesis (56) with the rest being used in processes such as transamination, or energy delivery (57). Given that ALT is a transaminase enzyme, it seems plausible to suggest that the small increases identified may represent increased transamination activity due to elevated BA availability. Alternatively, it is widely recognised that ALP and ALT are non-specific biomarkers, impacted by a range of factors, including physical activity (58). Given that BA supplementation is widely recognised to increase capacity for performance of high-intensity exercise, another potential explanation

for this finding may be increased activity within the BA group. These suggestions are of course speculative, and further research on the broader metabolic consequences of BA supplementation is required to enhance understanding in this area.

Effect of BA supplementation on taurine and histidine

The meta-analysis conducted on animal trials provides strong evidence that BA supplementation can cause a reduction in tissue taurine content at high doses (defined here as at least 3% solution in drinking water; ES: -2.71, 95%CrI: -3.33, -2.15), but not at lower doses (defined as <3% in drinking water, -0.32, 95%CrI: -0.80, 0.14). No evidence of an effect of BA supplementation on taurine content was identified in humans (ES: 0.002; 95%CrI: -0.48; 0.47). This is likely due to the substantially lower dose typically used in the human studies, when compared to the animal studies. The highest dose used in human studies was 6.4g·day^{-1} (39). For an 80kg male, this is the equivalent of 80mg·kg·day^{-1}. Assuming that a typical adult male mouse or rat weighs 25 or 400g respectively, and drinks 0.15 or 0.1 ml·g·day^{-1}, this would equate to an intake of 4500 or 3000 mg·kg·day^{-1} for a mouse or rat who is provided 3%BA in drinking water, which is ~34 – 53 fold greater than the typical human dose provided. Direct murine-to-human inferences are limited due to vastly different metabolic rates along with species-specific biochemistry, however, the available evidence does appear to indicate that the daily dose typically used in human studies (~ 3.2 - 6.4 g·day^{-1}) is not of the magnitude required to measurably reduce muscle taurine content.

No effect of total cumulative dose (TCD), nor of an interaction between TCD and daily dose, was obtained, indicating that intervention duration does not moderate the influence of BA on taurine, and that this effect does not increase over time. Lake et al (1988) reported that cardiac taurine content in rats was significantly reduced after 1, 2 and 3 weeks of treatment with 3%

BA in drinking water, although the magnitude of effect was smaller after 3 weeks compared to that identified at weeks 1 and 2, while after 6 weeks of treatment the BA group were not different to the pair-fed control animals (59). These data suggest that not only does the influence of BA not increase with time, it may in fact be reversed. Recently, a down-regulation of the BA/taurine transporter *Tau-T* was reported in humans ingesting $6.4 g \cdot day^{-1}$ of BA for 24 weeks (5), which may potentially represent a means of maintaining taurine homeostasis during periods of elevated BA availability. Further research is required to elucidate the mechanistic pathways through which both carnosine and taurine are regulated during BA supplementation.

Recently, it has been reported that BA supplementation may reduce plasma and muscle free histidine availability (17) and this was suggested as having potentially adverse consequences for muscle protein synthesis. The current meta-analysis showed no main effect of BA supplementation on histidine, in either human or murine models. It is important to highlight, however, that limited animal data was available, and the only animal study available investigated the influence of $100 mg \cdot kg^{-1}$ BA on brain histidine content (55). An influence of higher BA doses, as was observed in the taurine meta-analysis, or an influence on other tissues, cannot therefore, be ruled out.

The animal data described in Supplementary File 3 provided insight into the potential alterations to skeletal, cardiac, hepatic, renal and nervous function that may occur in response to very high BA doses used within these studies. Interestingly, the altered physiological processes described therein were neither exclusively positive nor negative in nature. For example, BA supplementation has been reported to exert both a protective (60) and a harmful (61) influence on cardiac function in rats, with limited consensus on the factors that dictate the nature of this response. An important limitation of many of the available animal studies, was that they typically focused on the influence of BA induced taurine deficiency, and rarely considered the broader actions of BA supplementation, which include increased carnosine, or

the independent action of BA *per se*. For example, Horvath et al. (2016) investigated the influence of taurine supplementation, and BA induced taurine depletion, on skeletal muscle contractility and fatigue resistance in wild-type and mdx mice (62), and reported that both interventions had a positive effect on muscle function. BA supplementation induced increases to muscle carnosine content are known to enhance skeletal muscle function and high-intensity exercise performance (2), and these results were likely due to increased carnosine, rather than to the taurine depletion that was reported. Conversely, Lu et al. (1996) reported a neuro-toxic influence of BA supplementation in cats, a species that are known to have a low capacity for endogenous taurine synthesis and to have a more severe and negative reaction to chronic BA supplementation. The authors identified that the neuro-toxicity that occurred in their study was due to BA accumulation, rather than to taurine depletion (63). The finding of a neuro-toxic influence of BA accumulation is also evident in humans suffering from the rare genetic condition "hyper-beta-alalinemia", which results in the accumulation of beta amino acids in the body (64). BA accumulation such as this is unlikely to occur in healthy humans, particularly in response to the doses commonly employed in practice, due to processes such as transamination, energy delivery (57), or incorporation into carnosine (4), and therefore is not considered a risk of supplementation. These examples do however, serve to highlight the importance of considering the broader influences of BA supplementation (*e.g.*, the independent influence of BA *per se*, along with collateral effects on other elements such as taurine, histidine and carnosine), when interpreting physiological results.

Side-effects experienced from BA intake in human trials

Paraesthesia was the only side-effect reported during human supplementation trials. This "tingling" or "pricking" sensation of the skin occurs as a result of a histamine independent neural pathway and is most likely induced upon binding of BA to the peripheral neuronal receptor MrgprD (65). This phenomenon is generally considered to be both transient and

harmless and appears not to be a cause for concern. Indeed some athletes have reported the sensation of paraesthesia to improve their affective response to exercise (43), although other participants in the same study reported the sensation to be uncomfortable or unpleasant, demonstrating that the experience of paraesthesia, and whether it should be considered a beneficial side effect or adverse effect, is a subjective experience that is specific to the individual. Collectively, the literature indicates that the development of paraesthesia is dose-related, and closely matches the extent and time to peak blood BA concentrations (4,44). Large heterogeneity in dosing studies used in longitudinal studies, along with minimal reporting of side-effects in many of the available studies precluded statistical identification of the most effective strategy to reduce the incidence of paraesthesia. However, acute studies indicated that the splitting of doses (4) or the use of sustained release capsules (44) may be an effective way to reduce the extent and/or time to peak blood BA concentration, and thus reduce or remove the occurrence and intensity of paraesthesia symptoms. Irrespective of dosing strategy used, was evidence of considerable within and between participant variability in the occurrence and intensity of paraesthesia development, and on-going investigation of the individual determinants of paraesthesia determinant would be of interest.

RECOMMENDATIONS FOR RESEARCH AND PRACTICE

The current investigation highlights a number of limitations and gaps in the current evidence base related to theoretical risks and physiological consequences of BA supplementation. Collectively, the assessment and reporting of side-effects in human studies were sub-optimal, thus limiting conclusions that can be drawn, and potentially causing an under-estimation of lower level side-effects experienced. Reliance on participant self-report is ill-advised, and it is stressed that researchers should, in future, employ pre-defined, systematic and objective means of side-effect assessment and reporting. Additionally, evidence of compliance to dosing protocols, including the spacing and timing of dosing throughout the day, is important to

identify whether or not strategies to reduce the occurrence of paraesthesia are effective. While no significant changes to any health-related biomarkers were identified in any of the individual studies that provided this data, statistical meta-analysis identified a main effect of BA supplementation on ALT, along with a trend toward increased ALP, although these markers remained well within clinical reference ranges. We suggest that further research should measure these markers, thus adding to the evidence base available. It is important to acknowledge that relatively limited data related to the influence of BA supplementation on taurine and histidine in humans is currently available, and it is possible that the available data-set may have been insufficient to allow detection of small changes. It is recommended that measurements of taurine and histidine, in addition to carnosine, are included in future studies. In recognition of the considerable individual variability in response to most sports nutrition based interventions, consideration of the individual response of participants to these parameters would be of interest (66). Additionally, over-simplistic interpretations of the physiological relevance of any observed changes should be avoided. Too often minimal nutrient or biomarker changes are dichotomously interpreted as being positive, or negative, which fails to acknowledge the complexity and interaction of these processes. Changes to the tissue content of these elements should be interpreted within the context of measured changes to relevant clinical or functional outcomes. In the absence of this information, findings should be neutrally interpreted and non-evidence-based speculations related to physiological consequences avoided.

DOSING RECOMMENDATIONS FOR HEALTHY HUMANS

According to the recommendations of the safety evaluation model used, if no data are available to establish adverse effects in humans, then a safe upper level of intake (UL) cannot be identified. This was the case within the current risk assessment, and so the highest observed limit with sufficient evidence of safety was used to guide recommendations. Recently, two

studies have been conducted using a dosing strategy of 12g·day^{-1} for a period of 7 (67) or 14 days (51), and no adverse effects were reported. Given the short follow-up of these studies, we recommend that intakes of 12g·day^{-1} should not yet be employed in general practice, pending further research. Intakes up to 6.4 g·day^{-1} were commonly used in the studies included within this review, and it is recommended that this intake should be adopted as the current highest observed limit (HOL) with sufficient evidence of safety. No evidence of adverse effects have been reported when doses at this level are consumed for up to 24 weeks (39). Importantly, much of the evidence described in the current risk assessment was conducted recently, with 95% of human studies published within the last 10 years. Should research continue at its current rate, it is likely that knowledge of the mechanistic actions and ergogenic and therapeutic potential of BA supplementation will substantially expand in the coming years. We recommend that information presented herein is continually updated based on emerging evidence, ensuring that dosing recommendations are made in accordance with the best quality and most recent evidence available.

SUMMARY AND CONCLUSIONS

The current comprehensive risk assessment of human and animal data revealed no adverse effects of BA supplementation in healthy humans, within the doses and durations described. Paraesthesia was the only reported side-effect, and no evidence exists to indicate that this phenomenon has any adverse consequences. Considerable within and between participant variability exists in relation to both the frequency and intensity of paraesthesia, although strategies to slow BA absorption, thus reducing the extent and time to peak plasma BA, can be used to reduce its occurrence and intensity. Although BA supplementation in high doses was shown to reduce tissue taurine content in animal models, the available human data showed no observable effect of BA supplementation on taurine, nor on muscle histidine. Collectively, the

available evidence indicates that BA supplementation, within the doses and durations described herein, is safe for human consumption.

Author Contribution:

ED and BG designed the research. ED and VP conducted all searches. BM BSH and FIS extracted all data. PS undertook all statistical analysis and data was analyzed by ED and BS. ED wrote the manuscript with ongoing criticial input from GA, BG, PS and BS. All authors read and approved the final manuscript.

REFERENCES:

1. Dolan E, Saunders B, Dantas W, Murai I, Roschel H, Artioli G, et al. A comparative study of hummingbirds and chickens provides mechanistic insight into the histidine containing dipeptide role in skeletal muscle metabolism. Sci Rep. 2018;in press.

2. Sale C, Artioli GG, Gualano B, Saunders B, Hobson RM, Harris RC. Carnosine: From exercise performance to health. Amino Acids. 2013;44(6):1477–91.

3. Boldyrev A, Aldini G, Derave W. Physiology and Pathophysiology of Carnosine. Physiol Rev [Internet]. 2013;93(4):1803–45. Available from: http://physrev.physiology.org/cgi/doi/10.1152/physrev.00039.2012

4. Harris RC, Tallon MJ, Dunnett M, Boobis L, Coakley J, Kim HJ, et al. The absorption of orally supplied β-alanine and its effect on muscle carnosine synthesis in human vastus lateralis. Amino Acids. 2006;30(3 SPEC. ISS.):279–89.

5. Saunders B, De Salles Painelli V, De Oliveira LF, Da Eira Silva V, Da Silva RP, Riani L, et al. Twenty-four Weeks of β-Alanine Supplementation on Carnosine Content, Related Genes, and Exercise. Vol. 49, Medicine & Science in Sports & Exercise. 2017.

896-906 p.

6. Saunders B, Elliott-Sale K, Artioli GG, Swinton PA, Dolan E, Roschel H, et al. β-alanine supplementation to improve exercise capacity and performance: a systematic review and meta-analysis. Br J Sports Med. 2017;51(8):658–69.

7. Maughan RJ, Burke LM, Dvorak J, Larson-Meyer DE, Peeling P, Phillips SM, et al. IOC consensus statement: Dietary supplements and the high-performance athlete. Br J Sports Med. 2018;52(7):439–55.

8. Artioli G, Sale C, Jones R. Carnosine in health and disease. Eur J Sport Sci. 2018;1–10.

9. Del Favero S, Roschel H, Solis MY, Hayashi AP, Artioli GG, Otaduy MC, et al. Beta-alanine (Carnosyn™) supplementation in elderly subjects (60-80 years): Effects on muscle carnosine content and physical capacity. Amino Acids. 2012;43(1):49–56.

10. De Marchis S, Modena C, Peretto P, Migheli A, Margolis F, Fasolo A. Carnosine-related dipeptides in neurons and glia. Biochem. 2000;65(7):824–33.

11. Dobrota D, Federova T, Stvolinksy S, Babusikova E, Likavcanova K, Drgova A, et al. Carnosine protects the brain of rats and Mongolian gerbils against ischemic injury: after-stroke-effect. Neurochem Res. 2005;30(10):1263–1238.

12. Renner C, Zemitzsch N, Fuchs B, Geiger KD, Hermes M, Hengstler J, et al. Carnosine retards tumor growth in vivo in an NIH3T3-HER2/neu mouse model. Mol Cancer [Internet]. 2010;9:2. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2818694&tool=pmcentrez&rendertype=abstract

13. Boldyrev A, Fedorova T, Stepanova M, Dobrotvorskaya I, Kozlova E, Boldanova N, et al. Carnisone increases efficiency of DOPA therapy of Parkinson's disease: A pilot study. Rejuvenation Res [Internet]. 2008;11(4):821–7. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=352246933

14. de Courten B, Jakubova M, de Courten M, Kukurova I, Vallova S, Krumpolec P, et al. Effects of carnosine supplementation on glucose metabolism: Pilot clinical trial.

561 Obesity. 2016;24(5):1027–34.

562 15. Kurata H, Fujii T, Tsutsui H, Katayama T, Ohkita M, Takaoka M, et al.
563 Renoprotective effects of l-carnosine on ischemia/reperfusion-induced renal injury in
564 rats. J Pharmacol Exp Ther. 2006;319(2):640–7.

565 16. Shaffer J, Kocsis J. Taurine mobilizing effects of beta alanine and other inhibitors of
566 taurine transport. Life Sci. 1981;28(24):2727–36.

567 17. Blancquaert L, Everaert I, Missinne M, Baguet A, Stegen S, Volkaert A, et al. Effects
568 of Histidine and β-alanine Supplementation on Human Muscle Carnosine Storage.
569 Med Sci Sport Exerc. 2017;49(3):602–9.

570 18. Hathcock J. Vitamin and Mineral Safety. Vitam Miner Saf. 2013;3rd. editi:1–190.

571 19. Shao A, Hathcock JN. Risk assessment for the amino acids taurine, l-glutamine and l-
572 arginine. Regul Toxicol Pharmacol. 2008;50(3):376–99.

573 20. Shao A, Hathcock JN. Risk assessment for creatine monohydrate. Regul Toxicol
574 Pharmacol. 2006;45(3):242–51.

575 21. Moher D, Liberati A, Tetzlaff J, Altman D, PRISMA. Preferred reporting items for
576 systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med.
577 2009;151(4):264–9.

578 22. Guyatt G, Oxman A, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE:
579 an emerging consensus on rating quality of evidence and strength of recommendations.
580 Br Med J (clinical Res ed). 2008;336(7650):924–6.

581 23. Welton N, Sutton A, Cooper A, Abrams K, Ades A. Meta-analysis using Bayesian
582 methods in Evidence synthesis for decision making in Healthcare. John Wiley Sons.
583 2012;76–93.

584 24. Morris S, DeShon R. Combining effect size estimates in meta-analysis with repeated
585 measures and independent-group designs. Psychol Methods. 2002;7(1):105–25.

586 25. Morris S. Estimating effect sizes from pretest-posttest- control group designs. Organ
587 Res Methods. 2008;11(2):364–86.

588 26. Zhang J, Ko C, Nie L, Chen Y, Tiwari R. Bayesian hierarchical methods for meta-

589 analysis combining randomized-controlled and single-arm studies. Stat Methods Med
590 Res. 2018;

591 27. Stout JR, Graves BS, Smith AE, Hartman MJ, Cramer JT, Beck TW, et al. The effect
592 of beta-alanine supplementation on neuromuscular fatigue in elderly (55-92 Years): a
593 double-blind randomized study. J Int Soc Sports Nutr. 2008 Nov;5.

594 28. McCormack WP, Stout JR, Emerson NS, Scanlon TC, Warren AM, Wells AJ, et al.
595 Oral nutritional supplement fortified with beta-alanine improves physical working
596 capacity in older adults: A randomized, placebo-controlled study. Exp Gerontol
597 [Internet]. The Authors; 2013;48(9):933–9. Available from:
598 http://dx.doi.org/10.1016/j.exger.2013.06.003

599 29. Glenn JM, Gray M, Stewart R, Moyen NE, Kavouras SA, Dibrezzo R, et al.
600 Incremental effects of 28 days of beta-alanine supplementation on high-intensity
601 cycling performance and blood lactate in masters female cyclists. Amino Acids.
602 Springer Vienna; 2015;47(12):2593–600.

603 30. Allman B, Biwer A, Maitland C, DiFabio B, Coughlin E, Smith-Ryan A, et al. The
604 effect of short term beta alanine supplementation on physical performance and quality
605 of life in Parkinson's Disease: A pilot study. J Exerc Physiol online. 2018;21(1):1–13.

606 31. Bailey CH, Signorile JF, Perry AC, Jacobs KA, Myers ND. Beta-Alanine Does Not
607 Enhance the Effects of Resistance Training in Older Adults. J Diet Suppl [Internet].
608 Taylor & Francis; 2018;15(6):860–70. Available from:
609 https://doi.org/10.1080/19390211.2017.1406422

610 32. Furst T, Massaro A, Miller C, Williams BT, LaMacchia ZM, Horvath PJ. β-Alanine
611 supplementation increased physical performance and improved executive function
612 following endurance exercise in middle aged individuals. J Int Soc Sports Nutr.
613 Journal of the International Society of Sports Nutrition; 2018;15(1):1–8.

614 33. Brisola GMP, Artioli GG, Papoti M, Zagatto AM. Effects of four weeks of β-alanine
615 supplementation on repeated sprint ability in water polo players. PLoS One [Internet].
616 2016;11(12):1–13. Available from: http://dx.doi.org/10.1371/journal.pone.0167968

617 34. Claus G, Redkva P, Brisola G, Malta E, de Araujo Bonetti de Poli R, Miyagi W, et al.
618 Beta-Alanine Supplementation Improves Throwing Velocities in Repeated Sprint

Ability and 200-m Swimming Performance in Young Water Polo Players. Pediatr Exerc Sci. 2017;29(2):203–12.

35. Milioni F, Redkva PE, Barbieri FA, Zagatto AM. Six weeks of β-alanine supplementation did not enhance repeated-sprint ability or technical performances in young elite basketball players. Nutr Health [Internet]. 2017;23(2):111–8. Available from: http://journals.sagepub.com/doi/10.1177/0260106017700436

36. de Andrade Kratz C, de Salles Painelli V, de Andrade Nemezio KM, da Silva RP, Franchini E, Zagatto AM, et al. Beta-alanine supplementation enhances judo-related performance in highly-trained athletes. J Sci Med Sport [Internet]. Sports Medicine Australia; 2017;20(4):403–8. Available from: http://dx.doi.org/10.1016/j.jsams.2016.08.014

37. Brisola G, de Souza Malta E, Santiago P, Vieira L, Zagatto A. Four weeks of b-alanine supplementation improves high-intensity game activities in water polo. Int J Physiol Perform. 2018;Epub(Epub):1–10.

38. Harris R, Kim H, Kim C, Kendrick I, Price K, Wise J. Simultaneous changes in muscle carnosine and taurine during and following supplementation with β-Alanine. Med Sci Sport Exerc. 2010;42(S5):107.

39. Saunders B, Franchi M, de Oliveira L, da Eira Silva V, Pires da Silva R, de Salles Painelli V, et al. 24-Wk β-Alanine Ingestion Does Not Affect Muscle Taurine Or Clinical Blood Parameters. 2017;Presented.

40. Kelly V. β–alanine: Performance effects, usage and side effects. Dr Thesis/ Univ Queensl. 2017;

41. Chung W, Shaw G, Anderson ME, Pyne DB, Saunders PU, Bishop DJ, et al. Effect of 10 week beta-alanine supplementation on competition and training performance in elite swimmers. Nutrients. 2012;4(10):1441–53.

42. Varanoske AN, Hoffman JR, Church DD, Coker NA, Baker KM, Dodd SJ, et al. Comparison of sustained-release and rapid-release β-alanine formulations on changes in skeletal muscle carnosine and histidine content and isometric performance following a muscle-damaging protocol. Amino Acids [Internet]. Springer Vienna; 2018;(0123456789):1–12. Available from: https://doi.org/10.1007/s00726-018-2609-4

649 43. Bellinger PM, Minahan CL. Performance effects of acute β-alanine induced
650 paraesthesia in competitive cyclists. Eur J Sport Sci. 2016;16(1):88–95.

651 44. Décombaz J, Beaumont M, Vuichoud J, Bouisset F, Stellingwerff T. Effect of slow-
652 release β-alanine tablets on absorption kinetics and paresthesia. Amino Acids.
653 2012;43(1):67–76.

654 45. Glenn J, Smith K, Moyen N, Binns A, Gray M. Effects of Acute Beta-Alanine
655 Supplementation on Anaerobic Performance in Trained Female Cyclists. J Nutr Sci
656 Vitaminol (Tokyo) [Internet]. 2015;61(2):161–6. Available from:
657 https://www.jstage.jst.go.jp/article/jnsv/61/2/61_161/_article

658 46. MacPhee S, Weaver I, Weaver D. An Evaluation of Interindividual Responses to the
659 Orally Administered Neurotransmitter ?-Alanine. J Amino Acids. 2013;1–5.

660 47. Bex T, Chung W, Baguet A, Stegen S, Stautemas J, Achten E, et al. Muscle carnosine
661 loading by beta-alanine supplementation is more pronounced in trained vs. untrained
662 muscles. J Appl Physiol [Internet]. 2014;116(2):204–9. Available from:
663 http://jap.physiology.org/cgi/doi/10.1152/japplphysiol.01033.2013

664 48. Mor A. The Acute Effects of Beta-Alanine on Blood Gas of Athletes after Maximal
665 Research Journal of Pharmaceutical , Biological and Chemical Sciences The Acute
666 Effects of Beta-Alanine on Blood Gas of Athletes after Maximal. 2018;(July).

667 49. Stautemas J, Everaert I, Lefevere FBD, Derave W. Pharmacokinetics of β-Alanine
668 Using Different Dosing Strategies. Front Nutr [Internet]. 2018;5(August):70. Available
669 from: https://www.frontiersin.org/article/10.3389/fnut.2018.00070/full

670 50. Stellingwerff T, Anwander H, Egger A, Buehler T, Kreis R, Decombaz J, et al. Effect
671 of two β-alanine dosing protocols on muscle carnosine synthesis and washout. Amino
672 Acids. 2012;42(6):2461–72.

673 51. Church D, Hoffman J, Varanoske A, Wang R, Baker K, La Monica M, et al.
674 Comparison of Two β-Alanine Dosing Protocols on Muscle Carnosine Elevations. J
675 Am Coll Nutr. 2017;36(8):608–16.

676 52. da Silva RP, de Oliveira LF, Saunders B, de Andrade Kratz C, de Salles Painelli V, da
677 Eira Silva V, et al. Effects of β-alanine and sodium bicarbonate supplementation on the

estimated energy system contribution during high-intensity intermittent exercise. Amino Acids [Internet]. Springer Vienna; 2018;(0123456789):1–14. Available from: http://link.springer.com/10.1007/s00726-018-2643-2

53. Hill CA, Harris RC, Kim HJ, Harris BD, Sale C, Boobis LH, et al. Influence of β-alanine supplementation on skeletal muscle carnosine concentrations and high intensity cycling capacity. Amino Acids. 2007;32(2):225–33.

54. Varanoske A, Hoffman J, Church D, Wang R, Baker K, Dodd S, et al. Influence of Skeletal Muscle Carnosine Content on Fatigue during Repeated Resistance Exercise in Recreationally Active Women. Nutrients [Internet]. 2017;9(9):988. Available from: http://www.mdpi.com/2072-6643/9/9/988

55. Hoffman JR, Zuckerman A, Ram O, Sadot O, Stout JR, Ostfeld I, et al. Behavioral and inflammatory response in animals exposed to a low-pressure blast wave and supplemented with β-alanine. Amino Acids. Springer Vienna; 2017;49(5):871–86.

56. Stegen S, Blancquaert L, Everaert I, Bex T, Taes Y, Calders P, et al. Meal and beta-alanine coingestion enhances muscle carnosine loading. Med Sci Sports Exerc. 2013;45(8):1478–85.

57. Blancquaert L, Baba SP, Kwiatkowski S, Stautemas J, Stegen S, Barbaresi S, et al. Carnosine and anserine homeostasis in skeletal muscle and heart is controlled by β-alanine transamination. J Physiol. 2016;594(17):4849–63.

58. Pettersson J, Hindorff U, Persson P, Bengstsson T, Malmqvist U, Werkstrom V, et al. Muscular exercise can cause highly pathological liver function tests in healthy men. Br J Clin Pharmacol. 2008;65(2):253–9.

59. Lake N, De Marte L. Effects of beta-alanine treatment on the taurine and DNA content of the rat heart and retina. Neurochem Res [Internet]. 1988;13(10):1003–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=3146030%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed4&NEWS=N&AN=19010454

60. Allo S, Bagby L, Schaffer S. Taurine depletion, a novel mechanism for cardioprotection from regional ischemia. Am J Physiol. 1997;273(4 Pt2):1956–61.

61. Pansani MC, Azevedo PS, Rafacho BPM, Minicucci MF, Chiuso-Minicucci F, Zorzella-Pezavento SG, et al. Atrophic cardiac remodeling induced by taurine deficiency in wistar rats. PLoS One. 2012;7(7):1–6.

62. Horvath DM, Murphy RM, Mollica JP, Hayes A, Goodman CA. The effect of taurine and β-alanine supplementation on taurine transporter protein and fatigue resistance in skeletal muscle from mdx mice. Amino Acids. Springer Vienna; 2016;48(11):2635–45.

63. Lu P, Xu W, Sturman JA. Dietary β-alanine results in taurine depletion and cerebellar damage in adult cats. J Neurosci Res. 1996;43(1):112–9.

64. SCrIver C, Pueschel M, Davies E. Hyper-beta-alinemia associated with beta-aminoaciduria and y-aminobutyricaciduria, somnolence and seizures. N Engl J Med. 1966;274(12):635–43.

65. Liu Q, Sikand P, Ma C, Tang Z, Han L, Li Z, et al. Mechanisms of itch evoked by β-alanine. J Neurosci. 2012;32(42):14532–7.

66. Swinton P, Stephens Hemingway B, Saunders B, Gualano B, Dolan E. A statistical framework to interpret individual response to intervention: Paving the way for personalised nutrition and exercise prescription. Front Nutr. 2018;5(41).

67. Hoffman J, Gepner Y, Hoffman M, Zelicha H, Shapira S, Ostfeld I. Effect of high-dose, short-duration b-alanine supplementatin on circulating IL-10 concentrations during intense military training. J Strength Cond Res. 2018;00(00):1–4.

737 **Table 1:** Health-related biomarker response to BA supplementation

Marker	ES (95% Crl)	Tau (50% Crl)	Marker	ES (95% Crl)	Tau (50% Crl)
Albumin	-0.257 (-0.642, 0.130)	0.551 (0.420, 0.651)	***MCH***	0.078 (-0.248, 0.397)	0.205 (0.074, 0.283)
ALP	0.434 (-0.067, 0.811)	0.462 (0.325, 0.574)	***MCHC***	0.153 (-0.242, 0.512)	0.298 (0.129, 0.407)
ALT	0.274 (0.04, 0.527)	0.187 (0.08, 0.262)	***MCV***	0.014 (-0.291, 0.323)	0.189 (0.066, 0.262)
AST	0.056 (-0.74, 0.283)	0.207 (0.09, 0.292)	***Monocytes***	0.398 (-0.685, 1.479)	1.214 (0.765, 1.487)
Basophils	0.265 (-0.427, 0.946)	0.670 (0.390, 0.845)	***Neutrophils***	-0.400 (-0.820, 0.022)	0.288 (0.104, 0.394)
Bicarbonate	-0.116 (-1.241, 1.061)	0.817 (0.210, 0.971)	***Platelets***	-0.085 (-0.266, 0.101)	0.101 (0.040, 0.142)
CK	-0.165 (-0.537, 0.206)	0.270 (0.107, 0.372)	***Potassium***	-0.513 (-1.183, 0.250)	0.609 (0.299, 0.774)
Creatinine	-0.028 (-0.226, 0.173)	0.152 (0.057, 0.220)	***RBC***	-0.043 (-0.354, 0.265)	0.181 (0.066, 0.248)
Eosinophils	-0.080 (-1.745, 1.591)	2.357 (1.621, 2.785)	***RDW***	-0.053 (-0.584, 0.469)	0.325 (0.088. 0.398)
GFR	0.048 (-0.256, 0.346)	0.181 (0.063, 0.252)	***Sodium***	0.497 (-0.033, 1.063)	0.392 (0.132, 0.511)
Globulin	-0.028 (-0.265, 0.196)	0.153 (0.063, 0.214)	***Total Bilirubin***	-0.285 (-0.800, 0.212)	0.442 (0.232, 0.571)
Hematocrit	0.075 (-0.224, 0.375)	0.166 (0.060, 0.227)	***Total Protein***	0.066 (-0.186, 0.327)	0.209 (0.095, 0.292)

Hemoglobin	0.058 (-0.288, 0.392)	0.180 (0.057, 0.246)	***Urea***	0.178 (-0.881, 1.193)	0.861 (0.364, 1.064)
LDH	0.018 (-0.292, 0.335)	0.237 (0.094, 0.330)	***Uric Acid***	-0.110 (-0.410, 0.205)	0.209 (0.078, 0.291)
Lymphocytes	0.022 (-0.478, 0.507)	0.394 (0.168, 0.530)	***WBC***	-0.220 (-0.545, 0.093)	0.199 (0.072, 0.277)

738 ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate transaminase; CK: Creatine Kinase; GFR: Glomerular Filtration
739 Rate; LDH: Lactate dehydrogenase; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV:
740 Mean cell volume; RBC: Red blood cell; RDW: Red cell distribution width; WBC: White blood cell.

741 **FIGURE CAPTIONS:**

742 **Figure 1:** Search Flow Diagram

743 **Figure 2:** GRADE quality rating of outcomes from longitudinal (Panel A) and acute (Panel
744 B) trials

745 **Figure 3:** Forest plot displaying the influence of BA supplementation on taurine in humans.

746 **Figure 4:** Forest plot displaying the influence of BA supplementation (<3% in drinking
747 water) on taurine in murine cardiac or skeletal muscle.

748 **Figure 5:** Forest plot displaying the influence of BA supplementation (≥3% in drinking
749 water) on taurine in murine cardiac or skeletal muscle.

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Supplementary Data

Supplemental Table 1: Evidence from human longitudinal studies

Author (date)	Aim	Population (n)	Dosing Strategy (total dose)	Primary Outcome
Al Horani et al. (2017) (1)	To investigate if BA supplementation impacts anaerobic capacity parameters during a Wingate test.	Healthy and physically active, but non-specifically trained males (10) and females (6) aged 32.2 ± 4.8 yrs (BA: 8 (5M, 3F); PLA: 8 (5M, 3F))	7 day protocol comprising 5 $g \cdot day^{-1}$, with participants given the choice of dividing this into 2 or 3 daily doses (Total BA: 35g)	No information provided
Allman et al. (2018) (2)	To investigate the influence of BA supplementation on physical performance and quality of life in individuals who have parkinsons disease.	Men (13) and women (6) with Parkinsons disease, aged 68 ± 9 yrs (BA n = 9; PLA n = 10).	28 day protocol, comprising 4.8 $g \cdot day^{-1}$ provided as 3 daily doses (Total BA: 134.4 g)	No side-effects were reported.
Baguet et al. (2009) (3)	To investigate the magnitude of carnosine loading in response to β-alanine and the time course of subsequent unloading in different human skeletal muscle types.	Physically active but non-specifically trained males aged 22.6 ± 1.9 (BA: 8, PLA: 7)	35 - 42 day protocol, comprising 2.4$g \cdot day^{-1}$ for 2 days, 3.6$g \cdot day^{-1}$ for 2 days, then 4.8 $g \cdot day^{-1}$ for the remaining 31 - 38 days, provided as 6 daily doses (Total BA: 160.8 - 194.4g).	No side-effects reported.
Baguet et al. (2010) (4)	To investigate if β-alanine is ergogenic for a 2000m rowing test.	Elite Belgian rowers, competing at national or international level, (comprising 18 males and 1 female) aged 24.2 ± 5 (BA: 8 PLA: 9)	49 day protocol, comprising 5$g \cdot day^{-1}$ of BA, provided as 5 daily doses (Total BA: 245g).	No side-effects reported.
Baguet et al. (2010) (5)	To investigate if β-alanine supplementation can attenuate exercise-induced acidosis during high-intensity exercise.	Physically active but non-specifically trained males aged 21.5 ± 1.2 (BA: 7; PLA: 7)	28 day protocol, comprising 2.4 $g \cdot day^{-1}$ for 2 days, 3.6$g \cdot day^{-1}$ for 2 days, then 4.8$g \cdot day^{-1}$ for the remaining 24 days, provided as 6 daily doses (Total BA: 127.2).	No information provided
Bailey et al. (2018) (6)	To investigate the combined influence of BA supplementation and endurance training on anthropometric measures and physical function in older adults.	Older, healthy men and women aged 67.8 ± 6.7 yrs yrs, who were living independently (BA n = 13, PLA n = 14)	84 day protocol, comprising 3.2$g \cdot day^{-1}$, provided as 2 daily doses in sustained release tablets (Total BA: 268.8g)	No information provided.
Bassinello et al. (2018) (7)	To investigate the influence of BA supplementation on isotonic, isometric and isokinetic muscular endurance tests.	Young, healthy, omnivorous and resistance-trained men aged 24.5 ± 4 yrs (BA n = 9, PLA n = 11).	28 day protocol, comprising 6.4 $g \cdot day^{-1}$, provided as 4 daily doses in sustained release capsules (Total BA: 179.2 g)	No information provided.
Bech et al. (2017) (8)	To investigate the effect of BA on fatigue development during a	Elite male (10) and female (7) kayak rowers, competing at national and international level,	56 day protocol, comprising 80.$mg \cdot kg \cdot day^{-1}$, provided as 3 daily	One male participant in the BA group experienced mild

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	maximal voluntary contraction, a 2-min MVC and on kayak ergometer and repeated sprint performance (5 x 250 m kayak).	aged 21.4 ± 2.7 yrs (BA: 9; PLA: 8)	doses and using slow release capsules (Total BA: 392g)	paresthesia during the first week of the supplementation period.
Bellinger and Minahan (2016a) (9)	To investigate the effects of β-alanine supplementation, alone, or in combination with sprint interval training, on cycling performance.	Endurance trained male cyclists, aged 25.4 ± 7.2 (BA: 7; PLA: 7)	28 day protocol, comprising 6.4g·day^{-1}, provided as 4 daily doses followed by 1.2 g·day^{-1} maintenance for 5 weeks during training. (Total BA: 221.2g).	No side-effects reported.
Bellinger and Minahan (2016b) (10)	To investigate the metabolic consequences of β-alanine supplementation during exhaustive supramaximal cycling and 4000m cycling time trial performance.	Trained male cyclists, aged 24.5 ± 6.2 yrs (BA: 9; PLA: 8)	28 day protocol, comprising 6.4g·day^{-1}, provided as 4 daily doses (Total BA: 179.2g).	No information provided
Bellinger and Minahan (2016c) (11)	To investigate the effect of β-alanine supplementation on performance in cycling time trials of different lengths (1, 4 & 10-km).	Trained male cyclists, aged 24.8 ± 6.7 yrs (BA: 7; PLA: 7)	28 day protocol, comprising 6.4g·day^{-1}, provided as 4 daily doses (Total BA: 179.2g).	One participant reported mild symptoms of paresthesia.
Bellinger et al. (2012) (12)	To investigate the effect of β-alanine supplementation alone, or in combination with sodium bicarbonate, on high intensity cycling performance.	Trained male cyclists aged 25.4 ± 7.2 yrs (BA: 7; PLA: 7)	28 day protocol, comprising 65mg·kg·day^{-1}, provided as 4 daily doses (Total BA: 128.8g).	Two participants who took BA reported mild symptoms of paresthesia.
Belviranli et al. (2016) (13)	To investigate the effect of β-alanine supplementation alone, or in combination with creatine on oxidant and antioxidant status during high-intensity cycling.	Sedentary, but otherwise healthy men aged 21.7 ± 1.9 yrs (BA: 11; PLA: 11)	28 day protocol, comprising 3.2 g·day^{-1} for 22 days, provided as two daily doses, followed by 6.4g·day^{-1} for 6 days, provided as 4 daily doses (Total BA: 108.8g).	No information provided
Bex et al. (2014) (14)	To investigate the effect of β-alanine on muscle carnosine content in different limbs, and in trained and untrained individuals.	Healthy non-athletes (10), road cyclists (10), swimmers (10) and flat water kayakers (5), aged 22 ± 1 yrs (BA: 35)	23 day protocol, comprising 6.4 g·day^{-1} provided as 4 daily doses (Total BA: 147.2g).	No side-effects reported.
Bex et al. (2015) (15)	To investigate if high volume and/or high intensity training can improve BA induced carnosine loading.	Healthy, non-specifically trained males (28) aged 21.78 ± 1.9 yrs, all of whom took the BA supplement.	23 day protocol, comprising 6.4 g·day^{-1} provided as 4 daily doses and using slow release capsules (Total BA: 147.2g).	No side-effects reported.

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Black et al. (2018) (16)	To investigate the influence of BA supplementation on muscle carnosine, muscle pH and the power-duration relationship.	Healthy male subjects aged 22 ± 3 yrs (BA n = 10, PLA n = 10).	28 day protocol, comprising 6.4 $g \cdot day^{-1}$, provided as 4 daily doses in sustained release tablets (Total BA: 179.2g)	No subject reported any adverse effect of supplementation.
Blanquaert et al. (2017) (17)	To investigate the independent and combined effects of BA and histidine supplementation on carnosine loading.	Healthy, non-specifically trained males (15) and females (15) aged 20 ± 2.4 yrs (BA: 10; HIS: 10; BA + HIS: 10) . 5M and 5F in each group.	23 day protocol, comprising $6g \cdot day^{-1}$ of BA or $4.7g \cdot day^{-1}$ of HIS or a combination of both supplements, all of which were provided as 6 daily doses (Total BA: 138g).	No information provided.
Brisola et al. (2016) (18)	To investigate the effect of β-alanine supplementation on repeated sprint ability in water polo players.	Well-trained male water polo athletes, aged 18 ± 4 (BA: 11; PLA: 11)	28 day protocol, comprising 4.6 $g \cdot day^{-1}$ for 10 days, provided as 6 daily doses, followed by 6.4 $g \cdot day^{-1}$ for 18 days, provided as 4 daily doses (Total BA: 163.2g).	3 participants in the β-A group and 1 in the placebo group reported paresthesia.
Brisola et al. (2018) (19)	To investigate the influence of BA supplementation on distance covered, time in different speed zones and sprint numbers during a simulated water polo game.	Young, male, well-trained water polo athletes, aged 16 ± 1 yrs (BA n = 6, PLA n = 5).	28 day protocol, with the first 10 days comprising 4.8 $g \cdot day^{-1}$ provided as 6 daily doses, followed by 18 days of 6.4 $g \cdot day^{-1}$, provided as 4 daily doses in sustained release capsules (Total BA: 163.2g)	No information provided.
Carpentier et al. (2015) (20)	To investigate the effect of β-alanine supplementation, in combination with high intensity training on strength and plyometric performance.	Healthy, physically active male (12) and female (15) physical education students, aged 21.7 ± 2.1 (BA: 14, 6 M, 8 F; PLA: 13, 6M 7F)	56 day protocol, comprising 5.6 $g \cdot day^{-1}$ provided as 7 daily doses (Total BA: 313.6g).	No side-effects reported.
Caruso et al. (2014) (21)	To investigate the effect of β-alanine supplementation on response to supramaximal lower body exercise performance.	Healthy, untrained college aged males (6) and females (4), (BA: 10; PLA: 10)	30 day protocol, comprising $3g \cdot day^{-1}$, provided as 5 daily doses (Total BA: 90g).	No side-effects reported.
Carvalho et al. (2018) (22)	To investigate the influence of exercise and BA supplementation on carnosine-aldehyde adducts.	Male cyclists aged 36 ± 6 yrs (BA n = 14, PLA n = 14).	28 day protocol, comprising 6.4 $g \cdot day^{-1}$ provided as 4 daily doses in sustained release capsules (Total BA: 179.2g)	No information provided.
Chung et al. (2012) (23)	To investigate the effect of β-alanine supplementation on swimming training and competition performance.	Elite/sub-elite swimmers (34 men and 26 females), representing all competitive strokes and distances, aged 21.7 ± 2.8 (BA: 22; PLA: 12)	28 day protocol, comprising 4.8 $g \cdot day^{-1}$ for 28 days provided as 3 daily doses, followed by $3.2g \cdot day^{-1}$ provided as 2 daily doses for 42 days (Total BA: 268.8g).	10 of the 22 respondents from the β-A group reported mild paresthesia.

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Chung et al. (2014) (24)	To investigate the effect of β-alanine supplementation on cycling time trial performance.	Well trained male cyclists/triathletes, aged 30.9 ± 7.7 (BA: 14; PLA: 13)	42 day protocol, comprising 6.4g·day^{-1}, provided as 4 daily doses (Total BA: 268.8g).	No side-effects reported.
Church et al. (2017) (25)	To compare 6 and 12 g·day^{-1} for 28 and 14 days on changes in carnosine, histidine and BA in both muscle and plasma.	Physically active males (18) and females (12) aged 23.77 ± 3 yrs (BA: 17; PLA: 8) .	28 day protocol of 6 g·day^{-1} or 14 days of 12 g·day^{-1} of BA, provided as 3 x 2g or 3 x 4 g daily doses (Total BA: 168g).	Paresthesia was the only side-effect reported, and the number of individuals reporting did not differ between the groups (p = 0.483), namely 1 participant in PLA; 3 in the 6g group and 2 in the 12g group.
Claus et al. (2016) (26)	To investigate the effect of β-alanine supplementation on water polo specific tests.	Trained, post-pubertal water polo players, aged 16 ± 2 (BA: 8; PLA: 7)	42 day protocol, comprising 6.4g·day^{-1}, provided as 4 daily doses (Total BA: 268.8g).	No information provided
Cochran et al. (2015) (27)	To investigate the effect of β-alanine on sprint interval training induced skeletal muscle adaptation and performance.	Physically active, but non-specifically trained males, aged 22.5 ± 2 (BA: 12; PLA: 12)	70 day protocol, comprising 3.2g·day^{-1} provided as two daily doses via slow release tablets (Total BA: 224g).	No information provided
Da Silva et al. (2018) (28)	To investigate the influence of BA supplementation on bioenergetic contribution during high intensity intermittent exercise, and on cycling time-trial (1km) performance.	Trained cyclists aged 38 ± 8.1 yrs (BA n = 36, PLA n = 35)	28 day protocol, comprising 6.4 g·day^{-1} provided as 4 daily doses in sustained release capsules (Total BA: 179.2g)	Three volunteers reported paresthesia with BA.
Danaher et al. (2014) (29)	To investigate the effect of the of β-alanine supplementation alone, or in combination with sodium bicarbonate on high intensity exercise performance.	Recreationally active males, aged 26.2 ± 1.9 yrs, (BA: 8; PLA: 8)	42 day protocol, comprising 4.8g·day^{-1} for 28 days, provided as 6 daily doses, followed by 6.4 g·day^{-1} for 14 days provided as 8 daily doses (Total BA: 224g).	No information provided
Del Favero et al. (2012) (30)	To investigate the effects of β-alanine supplementation on muscle carnosine content and exercise capacity in elderly subjects.	Older adults, who were not engaged in an exercise program, aged 64.7 ± 5 (BA: 12; PLA: 6)	84 day protocol, comprising 3.2g·day^{-1} provided as 2 daily doses in slow release capsules (Total BA: 268.8g).	No side-effects reported.
Derave et al. (2007) (31)	To investigate the effect of β-alanine supplementation on sprint fatigue and performance.	Well-trained male track and field athletes, aged 21.3 ± 4.2 (BA: 8; PLA: 7)	28-35 day protocol, comprising 2.4g·day^{-1} for 4 days, followed by 3.6g·day^{-1} for 4 days, then 4.8g·day^{-1} for the remaining 20-27 days,	No side-effects reported.

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			provided as 6 daily doses (Total BA: 120 - 153.6g).	
Donovan et al. (2012) (32)	To investigate the effect of β-alanine supplementation on boxing punch performance.	Amateur, competitive boxers, aged 25 ± 4 yrs (BA: 8; PLA: 8)	28 day protocol, comprising 6g·day^{-1} provided as 4 daily doses (Total BA: 168g)	No side-effects reported.
Ducker et al. (2013a) (33)	To investigate the effect of β-alanine supplementatino on 800-m track running performance.	Trained, recreational club runners, aged 22 ± 5.4 (BA: 9; PLA: 9)	28 day protocol, comprising 80mg·kg·day^{-1} provided as 4 daily doses (Total BA: 162.4).	No information provided
Ducker et al. (2013b) (34)	To investigate the effect of β-alanine supplementation, alone or in combination with sodium bicarbonate on repeated sprint performance.	Competitive intermittent team sport male athletes aged 21 ± 4.5 (BA: 6; PLA: 6)	28 day protocol, comprising 80mg·kg·day^{-1} provided as 4 daily doses via slow release capsules (Total BA: 187.6g).	No information provided
Ducker et al. (2013c) (35)	To investigate the effect of β-alanine supplementation on 2,000-m rowing ergometer performance.	Competitive male rowers aged 26 ± 9 (BA: 7; PLA: 9)	28 day protocol, comprising 80mg·kg·day^{-1} provided as 4 daily doses via slow release capsules (Total BA:187.6g).	No information provided
Ghiasvand et al. (2012) (36)	To investigate the effects of β-alanine supplementation on endurance performance.	Physically active male physical education students, aged 21.5 ± 5.1 (BA: 20; PLA: 19)	42 day protocol, comprising 2g·day^{-1} provided as 5 daily doses (Total BA: 84g).	No side-effects reported.
Eilaki et al. (2018) (37)	To investigate the influence of BA supplementation on ventilatory thresholds.	Male amateur swimmers aged 31.5 ± 8 (BA n = 6, PLA n = 8).	14 day protocol, comprising 2.3 g·day^{-1} for 7 days, followed by 4.6 g·day^{-1} for 7 days, provided as 2 daily doses (Total BA: 48.3g)	No information provided
Furst et al. (2018) (38)	To investigate the influence of BA supplementation on exercise endurance and executive function.	Middle aged, healthy and non-specifically trained men (8) and postmenopausal women (4) aged 60.5 ± 8.6 yrs (BA n = 7, PLA n = 5)	28 day protocol, comprising 2.4 g·day^{-1} provided as 3 daily doses (Total BA: 67.2g)	There were no subject complaints of paresthesia.
Glenn et al.(2015a) (39)	To investigate the effects of β-alanine on high intensity cycling performance.	Trained female masters cyclists, aged 53.3 ± 1 (BA: 11; PLA: 11)	28 day protocol, comprising 3.2g·day^{-1} provided as 4 daily doses (Total BA: 89.6g).	One subject reported feelings of paresthesia.
Greer et al. (2016) (40)	To investigate the effect of β-alanine supplementation on endurance performance.	Aerobically trained males aged 28.8 ± 9.8 yrs (BA: 7; PLA: 7)	30 day protocol, comprising 3g·day^{-1} for 7 days, followed by 6g·day^{-1} for 23 days, all provided as 4 daily doses (Total BA: 159g).	One participant reported paresthesia, but they were in the placebo group.
Gross et al. (2014a) (41)	To investigate the effect of β-alanine on high intensity and plyometric performance.	Elite male alpine skiiers, aged 19.5 ± 1.1 (BA: 5; PLA: 4)	35 day protocol comprising 4.8g·day^{-1} provided as three daily doses (Total BA: 168g).	Four out of the 5 subjects receiving BA reported no side effects. One participant reported having frequent and

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				severe paresthesia as well as some digestion problems.
Gross et al.(2014b) (42)	To investigate the effects of β-alanine supplementation and HIT on high intensity exercise performance.	Male athletes, competing in endurance, team or combat sports, aged 31 ± 8 (BA: 6; PLA: 9)	38 day protocol, comprising 3.2g·day^{-1} provided as 4 daily doses (Total BA: 121.6g).	No information provided
Hannah et al. (2015) (43)	To investigate the effect of β-alanine supplementation on in vivo contractile properties and voluntary neuromuscular performance.	Moderately active, but non-specifically trained males, aged 25.8 ± 6.4 (BA: 12; PLA: 11)	28 day protocol, comprising 6.4g·day^{-1}, provided as 4 daily doses via slow release capsules (179.2g).	No side-effects reported.
Harris et al. (2006) (44)	To investigate the bioavailability of oral β-alanine supplementation and its effect on muscle carnosine synthesis.			
PART B	To investigate the effect of 2 weeks of β-alanine intake.	Male subjects, aged 28.3 ± 2.7 yrs (BA: 6)	14 day protocol, comprising 30mg·kgBM·day^{-1}, provided as 3 daily doses (Total BA:34.3g).	Occasional reports of mild flushing were reported.
PART C	To investigate the effect of 4 weeks β-alanine supplementation on blood biochemistry and haematology.	Male subjects, aged 19.4 ± 1.6 yrs (BA: 8; PLA: 8)	28 day protocol, comprising 3.2g·day^{-1} provided as 4 daily doses (Total BA:89.6g).	No information provided.
PART D	To investigate the effect of 4 weeks β-alanine supplementatino on muscle carnosine content.	Male subjects aged 26.1 ± 5.6 yrs (21 total; 10 BA, 5 CARN, 6 PLA)	Treatment 1: 28 day protocol comprising 3.2g·day^{-1} provided as 4 daily doses (Total BA:89.6g). Treatment 2: 28 day protocol comprising 4g·day^{-1} for the first week, with doses increasing each week so that in week 4 participants ingested 6.4g·day^{-1}, all provided as 8 daily doses (Total BA: 145.6g). Treatment 3: Equal to T2, however β-A was provided in the form of L-carnosine (Total BA: 143.3g). Treatment 4: placebo.	Mild symptoms of flushing were reported in week 2 by 4 of the subjects given BA, while one subject given placebo also recorded mild symptoms of flushing.
Hill et al.(2007) (45)	To investigate the effect of β-alanine supplementation on high intensity cycling capacity.	Physically active, but non-specifically trained males, aged 27.2 ± 5.3 (4 weeks - BA: 13; PLA: 12; 10 weeks - BA: 7; PLA: 8)	70 day protocol, comprising 4 g·day^{-1} for 7 days, 4.8g·day^{-1} for 7 days, 5.6g·day^{-1} for 7 days and 6.4g·day^{-1}	Reports of symptoms of paresthesia were infrequent and mild when they occurred.

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			for the final 49 days, all provided as 8 daily doses (Total BA: 4 weeks: 145.6g; 10 weeks: 414.4g)	
Hobson et al.(2013) (46)	To investigate the effect of β-alanine alone, or in combination with sodium bicarbonate on 2000m rowing performance.	Trained, competitive club level rowers aged 23 ± 4 (BA: 10; PLA: 10)	30 day protocol, comprising 6.4g·day^{-1} provided as 4 daily doses via slow release capsules (Total BA: 192g).	No side-effects reported.
Hobson et al. (2014) (47)	To investigate the effect of β-alanine on 20km time trial performance.	Well-trained male cyclists aged 33.7 ± 7, (BA: 10; PLA: 9)	28 day protocol, comprising 6.4g·day^{-1} provided as 4 daily doses via slow release capsules (Total BA: 179.2g).	No side-effects reported.
Hoffman et al. (2008a) (48)	To investigate the effect of β-alanine supplementation on resistance training volume and the acute endocrine response to resistance exercise.	Resistance trained males aged 19.7 ± 1.5yrs (BA: 8; PLA: 8)	28 day protocol comprising 4.8g·day^{-1} provided as 3 daily doses (Total BA: 134.4g).	No information provided
Hoffman et al. (2008b) (49)	To investigate the effect of β-alanine supplementation on training volume and anaerobic exercise performance.	Strenth/power trained male athletes, aged 19.8 ± 1.6 (BA: 13; PLA: 13)	30 day protocol comprising 4.5g·day^{-1} provided as 3 daily doses (Total BA: 135g).	No information provided
Hoffman et al. (2014) (50)	To investigate the effect of β-alanine supplementation on physical and cognitive performance.	Male soldiers from an elite combat unit of the Israel Defense Forces aged 20.2 ± 0.9 (BA: 9; PLA: 9)	28 day protocol comprising 6g·day^{-1} provided as 3 daily doses (Total BA: 168g).	4 participants in the β-A group reported isolated incidences of paresthesia. No other adverse events were reported for any other participant.
Hoffman et al.(2015) (51)	To investigate the effect of β-alanine supplementation on combat specific activity.	Male soldiers from an elite combat unit of the Israel Defense Forces aged 19.9 ± 0.8 (BA: 9; PLA: 9)	30 day protocol comprising 6g·day^{-1} provided as 3 daily doses (Total BA: 180g).	No side-effects reported.
Hoffman et al. (2018) (52)	To investigate the influence of BA supplementation on anti-inflammatory cytokines during intense military training.	Male soldiers from an Israel Defence Force elite combat unit, aged 20.1 ± 0.6 yrs (BA n = 10, PLA n = 10).	7 day protocol comprising 12 g·day^{-1}, provided as 3 daily doses in sustained release capsules (Total BA: 84g)	Of those participants who were excluded from final analyses for non-compliance, one experienced side effects (itching and flushing).
Howe et al.(2013) (53)	To investigate the effect of β-alanine supplementation on 4 min maximal cycling performance and isokinetic knee-extension.	Highly trained male cyclists aged 24 ± 6.8 (BA: 8; PLA: 8)	28 day protocol comprising 65mg·kg·day^{-1} provided as 4 daily doses (Total BA: 127.4g)	2 participants in the β-A group reported paresthesia.
Jagim et al.(2013) (54)	To investigate the effect of β-alanine supplementation on sprint	Trained men comprising wrestlers (11), recreationally strength trained athletes (6) and	35 day protocol comprising 4g·day^{-1} for 7 days followed by 6g·day^{-1} for	No information provided

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	endurance at two different supramaximal intensities.	rugby players (4) aged 20 ± 2.3 (BA: 10; PLA: 11)	the remaining 28 days, all provided as 3 daily doses (Total BA: 196g) .	
Jones et al. (2017) (55)	To investigate the effect of β-alanine supplementation on knee extensor force production and muscle contractility in fresh and fatigued human muscle, during voluntary and electrically evoked contractions.	Non-specifically trained males aged 22 ± 1.5 (BA: 12; PLA: 11)	28 day protocol comprising 6.4g·day^{-1} provided as 4 daily doses (Total BA: 179.2g).	No side-effects reported.
Jordan et al.(2010) (56)	To investigate the effect of β-alanine supplementation on the onset of blood lactate accumulation (OBLA) during incremental treadmill running.	Recreationally active runners aged 24.9 ± 4.5 (BA: 8; PLA: 9)	28 day protocol, comprising 6g·day^{-1} provided as 3 daily doses (Total BA: 168g).	3 participants in the β-A group reported tingling in their fingers and hands (paresthesia).
Kendrick et al. (2008) (57)	To investigate the effect of β-alanine supplementation on training induced resistance responses.	Fit and healthy non-resistance trained physical education students aged 21.5 ± 2 (BA: 13; PLA: 13)	28 day protocol comprising 6.4g·day^{-1} provided as 8 daily doses (Total BA: 179.2g).	No information provided
Kendrick et al. (2009) (58)	To investigate the effect of isolateral training with, and without β-alanine supplementation on muscle carnosine content.	Fit and healthy physical education students aged 21.9 ± 2.6 (BA: 7; PLA: 7)	28 day protocol comprising 6.4g·day^{-1} provided as 8 daily doses (Total BA: 179.2g).	No information provided
Kern and Robinson. (2011) (59)	To investigate the effect of β-alanine supplementation with high intensity training on anaerobic power and body composition.	NCAA division II college wrestlers and American Footballers aged 19.4 ± 1.8. (BA: 17; PLA: 20)	56 day protocol comprising 4g·day^{-1} provided as 2 daily doses (Total BA: 224g).	No information provided
Kratz et al. (2016) (60)	To investigate the effect of β-alanine supplementation on judo performance.	Well-trained male judo competitors aged 17.9 ± 2.7 (BA: 12; PLA: 11)	28 day protocol comprising 6.4g·day^{-1} provided as 4 daily doses(Total BA: 179.2g).	1 participant in the β-A group, and one in the placebo group reported mild paresthesia.
Kresta et al. (2014) (61)	To investigate the effect of β-alanine supplementation only, or with creatine, on anaerobic performance.	Healthy, moderately active females aged between 18 and 35 (BA only 8, PL: 7)	28 day protocol comprising 0.1g·kg·day^{-1} provided as 4 daily doses (Total BA: 170.8g)	No information provided
Mate-Munoz et al. (2018) (62)	To investigate the influence of BA supplementation during a resistance training program on strength and power outcomes.	Young, healthy, resistance-trained men aged 18 - 25 yrs (BA n= 14, PLA n = 12)	35 day protocol, comprising 6.4 g·day^{-1} provided as 8 daily doses, taken alongside a resistance training program (Total BA: 224g)	No information provided.
McCormack	To investigate the effect of an oral	Older men and women aged 71.2 ± 6.3 (BA:	84 day protocol comprising 1.6 or	6 participants in the 2.4g.day-

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et al. 2013 (63)	nutritional supplement fortified with β-alanine on body composition, muscle function and physical capacity in older adults.	(BA: 28; PLA: 16).	2.4g·day^{-1} provided as 2 daily doses with an oral nutritional supplement (Total BA: 134.4 - 201.6g).	1 group, and 1 from the 1.6g.day-1 group reported paresthesia. 2 of the dropouts from the 2.4g.day-1 group cited paresthesia as the reason for withdrawal.
Mero et al. (2013) (64)	To investigate the effect of β-alanine supplementation alone, or with sodium bicarbonate on maximal sprint swimming.	National and international male swimmers aged 20.5 ± 1.4 yrs (BA: 13)	28 day protocol comprising 4.8g·day^{-1} provided as 8 daily doses (Total BA: 134.4).	All participants in the β-A group reported paresthesia.
Milioni et al (2017) (65)	To investigate the effect of β-alanine supplementation on repeated sprint ability and technical basketball performance.	Post-pubertal male basketball players aged 16-19 yrs (BA: 12; PLA: 10)	42 day protocol comprising 6.4g·day^{-1} provided as 4 daily doses (Total BA: 268.8g).	7 participants in the β-A group, and 3 in the placebo group reported isolated occurrences of mild paresthesia.
Outlaw et al. (2016) (66)	To investigate the effect of β-alanine supplementation during resistance training on aerobic & anaerobic performance and body composition.	Collegiate, non-specifically trained females aged 21 ± 2.2 yrs (BA: 7; PLA: 8).	56 day protocol comprising a single dose of 3.4g·day^{-1} prior to training 4 days·week^{-1} (Total BA: 108.8g).	No side-effects reported.
Painelli et al. (2013) (67)				
Part A	To investigate the effect of β-alanine supplementation on swimming performance	Junior standard male (12) and female (6) swimmers aged 19.3 ± 4.1 (BA: 9; PLA: 7)	35 day protocol comprising 3.2g·day^{-1} for 7 days, followed by 6.4g·day^{-1} for 28 days, all provided as 4 daily doses (Total BA: 201.6g).	4 participants in the β-A group reported mild paresthesia
Part B	To investigate the co-ingestion of β-alanine and sodium bicarbonate on swimming performance.	Junior standard male (7) and female (7) swimmers aged 19.7 ± 3.1 (BA: 7; PLA: 7)	32 day protocol comprising 3.2g·day^{-1} for 7 days, followed by 6.4g·day^{-1} for 25 days, all provided as 4 daily doses (Total BA: 182.4g).	4 participants in the β-A group reported mild paresthesia.
Painelli et al. (2014) (68)	To investigate the effect of β-alanine supplementation on high intensity exercise performance in trained and non-trained cyclists.	Endurance trained male cyclists (20) or non trained males aged 28.9 ± 8.3 (BA: 20; PLA: 19)	28 day protocol comprising 6.4g·day^{-1} provided as 4 daily doses (Total BA: 179.2g)	3 participants in the β-A group reported paresthesia.
Rosas et al. (2017) (69)	To investigate the effects of a plyometric training program, with and without BA supplementationo on maximal intensity and	Amateur female soccer platers (25) aged 23.7 ± 2.4 yrs (BA: 8; PLA: 17)	42 day protocol comprising 4.8g·day^{-1} provided as 6 daily doses (Total BA: 201.6g).	Five athletes in the BA group reported mild paresthesia symptoms

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	endurance performance in female soccer players.			
Sale et al.(2011) (70)	To investigate the effect of β-alanine supplementation only, and with sodium bicarbonate supplementation on high intensity cycling capacity.	Physically active males accustomed to high intensity exercise aged 24.5 ± 4.1 (BA: 10; PLA: 10)	28 day protocol, comprising 6.4g·day^{-1} provided as 4 daily doses (Total BA: 179.2g).	No information provided.
Sale et al.(2012) (71)	To investigate the effect of β-alanine supplementation on submaximal isometric endurance of the knee extensor muscles.	Physically active males aged 23 ± 6 (BA: 7; PLA: 6)	28 day protocol comprising 6.4g·day^{-1} provided as 8 daily doses (Total BA: 179.2g).	No information provided.
Santana et al. (2018) (72)	To investigate the influence of BA supplementation on 10km running time trial performance.	Healthy, male runners aged 29.4 ± 3.9 yrs (BA n = 8, PLA n = 8).	23 day protocol comprising 5g.day-1 provided as 3 daily doses (Total BA: 115 g)	No information provided.
Saunders et al. (2012a) (73)	To investigate the effect of β-alanine supplementation on multiple sprint performance during the Loughborough Intermittent Shuttle Test (LIST)	Male elite hockey players and non-elite football or hockey players aged 20.7 ± 2.5 (BA: 18; PLA: 18)	28 day protocol comprising 6.4g·day^{-1} provided as 4 daily doses (Total BA: 179.2g).	No side-effects reported.
Saunders et al. (2012b) (74)	To investigate the effect of β-alanine supplementation on YoYo intermittent recovery test level 2 (YoYo IRL2) performance	Amateur male footballers aged 22 ± 4 yrs (BA: 9; PLA: 8)	84 day protocol comprising 3.2g·day^{-1} provided as 4 daily doses via slow release capsule (Total BA: 268.8g).	No side-effects reported.
Saunders et al. (2014) (75)	To investigate the effect of β-alanine supplementation only, or with sodium bicarbonate on repeated sprints performance in hypoxia.	Recreationally active male games players aged 22.5 ± 3.5 (BA: 8; PLA: 8)	25 day protocol comprising 6.4g·day^{-1} for 28 days, followed by 3.2g·day^{-1} for 7 days, all provided as 4 daily doses via slow release capsules (Total BA: 201.6g).	No side-effects reported.
Saunders et al. (2018) (76)	To investigate the effect of BA supplementation on muscle taurine, blood clinical markers and sensory side-effects.	Physically active healthy males aged 27 ± 4 (BA: 15; PLA: 8)	168 day protocol comprising 6.4g·day^{-1} provided as 4 daily doses (Total BA: 1075.2g).	No side-effects reported
Smith et al. (2009) (77)	To investigate the effect of β-alanine supplementation during HIIT on endurance performance and body composition.	Recreationally active men aged 22.2 ± 2.7 yrs (BA: 18; PLA: 18)	42 day protocol comprising 6g·day^{-1} for 21 days, followed by 3g·day^{-1} for 21 days (Total BA: 189g)	No information provided.
Smith et al.(2012a)	To investigate the effect of β-alanine supplementation on	Moderately trained healthy women aged 21.7 ± 2.1 (BA: 13; PLA: 11)	28 day protocol comprising 4.8g·day^{-1} provided as 3 daily doses (Total BA:	2 participants in the β-A group reported mild symptoms of

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(78)	markers of oxidative stress, and measures of aerobic performance in women.		134.4g).	paresthesia, reported as mild prickling on the back of the hands and face.
Smith-Ryan et al. (2012b) (79)	To investigate the effect of β-alanine supplementation on high-velocity intermittent running performance.	Recreationally active men and women aged 21.9 ± 2.8 (BA: 26; PLA: 24)	28 day protocol comprising 4.8g·day^{-1} provided as 3 daily doses (Total BA: 134.4g).	2 participants in the β-A group, and 3 in the placebo group reported mild paresthesia.
Smith-Ryan et al. (2014a) (80)	To investigate the effect of β-alanine supplementation on exercise induced oxidative stress in men.	Recreationally active males aged 21.9 ± 3.4yrs (BA: 12; PLA: 13)	28 day protocol comprising 4.8g·day^{-1} provided as 3 daily doses (Total BA: 134.4g).	No information provided.
Smith-Ryan et al.(2014b) (81)	To investigate the effect of β-alanine supplementation on physical working capacity at heart rate threshold.	Recreationally active men and women aged 21 ± 2.1 (BA: 15; PLA: 15)	28 day protocol comprising 6.4g·day^{-1} (Total BA: 179.2g).	No side-effects reported.
Solis et al. (2015) (82)	To investigate the effect of β-alanine supplementation brain homocarnosine/carnosine levels and cognitive function.			
PART A	To investigate the effect of β-alanine supplementation on brain carnosine content, assessed using 1H-MRS.	Healthy vegetarians (3 women and 4 men) and age and sex matched omnivores aged 29.7 ± 8.7 (BA: 14)	28 day protocol comprising 6.4g·day^{-1} provided as 4 daily doses (Total BA: 179.2g).	No information provided
Part B	To investigate the effect of β-alanine supplementation on cognitive function.	UK category 1 male cyclists aged 34.6 ± 7.4 (BA: 10; PLA: 9)	28 day protocol comprising 6.4g·day^{-1} provided as 4 daily doses (Total BA: 179.2g).	No information provided
Stegen et al. (2013) (83)				
PART A	To investigate the effect of 5-week BA supplementation with and without coingestion of carbohydrate and protein on whole body BA retention.	Men aged 22.1 ± 1.3 yrs (BA: 7)	35 day protocol comprising 4.8g·day^{-1} slow release BA provided as three daily doses (Total BA: 168g).	No information provided
PART B	To investigate the effect of meal timing on muscle carnosine loading.	Men (16) and women (18) aged 19.4 ± 1 yrs (BA: 34).	46 day protocol comprising 3.2g·day^{-1} provided as 4 daily doses (Total BA: 147.2g).	No information provided
Stellingwerf et al. (2012)	To investigate the effect of two different doses of β-alanine on the	Healthy male subjects, with baseline carnosine content >1 SD below mean Mcarn, aged 24.8 ±	Group High-Low: 3.2g·day^{-1} for 28 days, followed by 1.6g·day^{-1} for 28	16.4, 11.6 and 20% of participants reported unusual

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(84)	time course of muscle carnosine loading and subsequent 8 week washout.	4.5 (BA: 33)	weeks. Group Low - Low: 1.6g·day^{-1} for 56 days (Total BA: 89.6 - 134.4g).	sensations for the placebo, low-low and high-low groups respectively, and this was not significantly different between the groups. These unusual symptoms were most frequently located in the arms and shoulders. The placebo group reported more negative POMS and SAI ratings than either treatment group.
Stout et al. (2006) (85)	To investigate the effect of β-alanine supplementation only, or with creatine on physical working capacity at fatigue threshold.	Men aged 24.5 ± 5.3 (BA: 12; PLA: 13) .	28 day protocol, comprising 6.4g·day^{-1} for 6 days, provided as 4 daily doses, followed by 3.2g·day^{-1} for 22 days, provided as 2 daily doses (Total BA: 108.8g).	No information provided
Stout et al. (2007) (86)	To investigate the effect of β-alanine supplementation physical working capacity at fatigue threshold and endurance performance.	Women aged 27.4 ± 6.4 (BA: 11; PLA: 11)	28 day protocol, comprising 3.2g·day^{-1} for 7 days, followed by 6.4g·day^{-1} for 21 days, all provided as 3 daily doses (Total BA: 156.8g).	No information provided
Stout et al. (2008) (87)	To investigate the effect of β-alanine supplementation on physical working capacity at fatigue threshold in older adults.	Community dwelling older men and women, aged 72.8 ± 11.1 (BA: 12; PLA: 14)	90 day protocol, comprising 2.4g·day^{-1} provided as 3 daily doses (Total BA: 216g).	No information provided
Sweeney et al. (2010) (88)	To investigate the effect of β-alanine supplementation on repeat high-intensity sprint performance.	Physically active males, trained in either football or strength, aged 22.6 ± 1.5 (BA: 9; PLA: 10)	35 day protocol comprising 4g·day^{-1} for 7 days, followed by 6g·day^{-1} for 28 days, all provided as 3 daily doses (Total BA: 196g).	Subjects (number unspecified) reported mild paresthesia.
Tobias et al.(2013) (89)	To investigate the effect of β-alanine supplementation only, or with sodium bicarbonate on high intensity upper body intermittent exercise performance.	Well-trained male judo and jiu-jitsu athletes aged 26.4 ± 4.4 (BA: 10; PLA: 9).	28 day protocol, copmrising 6.4g·day^{-1}, provided as 4 daily doses (Total BA: 179.2g).	1 participant in the β-A group reported paresthesia.
Van Thienen et al. (2009) (90)	To investigate the effect of β-alanine supplementation on cycling performance.	Moderate to well-trained male cyclists, aged 24.9 (range 18 - 30; BA: 9; PLA; 8)	56 day protocol, comprising 2g·day^{-1} for 14 days, followed by 3g·day^{-1} for 14 days, then 4g·day^{-1} for the remaining 28 days, all provided in	No side-effects reported.

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			500mg capsules (Total BA: 182g) .	
Varanoske et al. (2017) (91)	To compare 28 days of BA supplementation in men and women on performance and muscle carnosine, histidine and BA	Recreationally active males (10) and females (10) (BA: 12 (6M, 6F); PLA: 8 (4M, 4F))	28 day protocol, comprising $6g \cdot day^{-1}$, provided as 3 daily doses using slow release capsules (Total BA: 168g).	No information provided
Varanoske et al. (2018) (92)	To investigate the influence of BA provided as sustained (SR) or rapid-release (RR) fomulations on muscle carnosine, BA and histidine, and on muscle performance.	Physically active men (15) and women (14) aged 22.7 ± 2.6 yrs (SR BA n = 12, RR BA n = 9, PLA n = 8)	28 day protocol, comprising $6\ g \cdot day^{-1}$ provided as 3 daily doses, as either a sustained, or rapid, release formulation (Total BA: 168g)	Paresthesia was the only reported side-effect, and occurred significantly more frequently (25.4 ± 4.8 days) in the RR group, than in either the SR (3.4 ± 8.4 days) or PLA groups (0.1 ± 0.4 days).
Walter et al.(2010) (93)	To investigate the effect of β-alanine supplementation during HIIT on endurance performance and body composition.	Healthy, recreationally active women aged 21.8 ± 3.5 (BA: 14; PLA: 19)	42 day protocol, comprising $6g \cdot day^{-1}$ for 21 days provided as 4 daily doses, followed by $3g.day^{-1}$ for 21 days provided as 2 daily doses (Total BA: 189g).	No information provided
Zoeller et al. (2007) (94)	To investigate the effect of β-alanine supplementation only, or with creatine on endurance performance.	Men aged 24.5 ± 5.3 yrs (BA: 14; PLA: 13).	28 day protocol, comprising $6.4g \cdot day^{-1}$ for 6 days, provided as 4 daily doses, followed by $3.2g \cdot day^{-1}$ for 22 days, provided as 2 daily doses (Total BA: 108.8g).	No information provided

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Supplemental Table 2: Evidence from human acute studies

Author (date)	Aim	Population (n)	Dosing Strategy	Primary Outcome
Bellinger et al. (2016) (95)	To investigate the effect of acute β-alanine ingestion on paresthesia symptoms, mood and psychological effects.	Well-trained male cyclists (8) aged 27.7 ± 5.9 years.	30mg·kgBM^{-1} (approx 1.98 g of BA)	β-alanine ingestion did not impact 1km cycling time trial performance. β-alanine caused a significant sensory response, with the sensation described as "tingling or pins and needles", and a trend toward increased vigour (p = 0.07-008). Two of the participants reported the sensations to be uncomforable or unpleasant. Five of the participants subjectively reported that paresthesia positively influenced their affective response to the time trial.
Decombaz et al. (2012) (96)	To investigate the effect of slow release β-alanine tablets on absorption kinetics and paresthesia.	Healthy males (6) and females (5) aged 26 ± 4 yrs.	1.6g provided in either slow release tablet form, or in pure aqueous solution.	Only βA in solution produced evident sensations, with the intensity described as "pins and needles". Sensory response globally and anticipatorily paralleled that of plasma βA concentration. Paresthesia symptoms were influenced by the extent and time to peak plasma βA concentration.
Glenn et al. (2015) (97)	To investigate the effect of acute β-alanine ingestion on anaerobic performance in trained female cyclists.	Trained competitive female cyclists (12) aged 26.6 ± 1.3 yrs.	1.6g + 34 g dextrose mixed with 16 ounces of water. Ingested 30 min prior to exercise.	One participant reported feelings of paraesthesia. Anaerobic performance was not impacted by supplementation, but the β-alanine reported lower perceived exertion during the repeated Wingate test.
Harris et al. (2006) (44)	To investigate the effect of acute administration of different forms of β-alanine on blood and urine bioavailability.	Healthy males (6) aged 33.5 ± 9.9 yrs.	0, 10, 20 or 40 mg·kgBM^{-1}, provided as chicken broth, or as pure β-alanine dissolved in water.	Pure β-alanine caused an "irritation of the skin or a prickly sensation", but chicken broth did not. This response was dose-dependent, with 40mg.kgBM-1 causing sensations that were considered unpleasant by all participants, and intolerable by 2, while the lower doses invoked similar feelings, but of milder intensities.
Kelly et al. (2017) (98)				
Part A	To determine if the acute side-effects resulting from β-A supplementation differed between	Healthy meat-eating males (15) aged 23.5 ± 7.6 stratified into groups based on body mass (< 75 VS >85kg)	1.6g (absolute dose) or 0.02g·kgBM^{-1} (relative dose) provided as powder dissolved in 10ml sugar free cordial. The mean relative dose corresponded to 1.33g for the lighter group, and	Lighter individuals had a reduced incidence and severity of symptoms when consuming the absolute dose, while the reverse was true for heavier individuals, who experienced a greater incidence and severity of symptoms when consuming the relative dose.

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	absolute and relative doses, and whether body mass and composition were related to side effects experienced.		1.84g for the heavier.	
Part B	To determine if paresthesia experienced following acute BA supplementation is related to high intensity exercise performance.	Recreationally trained males (12) aged 21.1 ± 4.2 yrs, who experienced paresthesia after ingestion of pure BA, but not after ingesting sustained released BA.	1.6g provided as either pure or sustained release BA.	Intensities and manifestations of side effects were highest in the pure BA condition, followed by the sustained release BA condition, then placebo ($p < 0.05$ for differences between each condition). Side-effects experienced were not related to performance outcomes. The occurrence of side-effects in individual participants were not consistent between trials.
MacPhee et al. (2013) (99)	To investigate the influence of ethnicity on the acute response to beta-alanine ingestion.	Asian (10), and Caucasian (10) men and women (ratio 7/3 in both groups), with mean age of 31 yrs.	3g dose, dissolved in 200ml of an artificial fruit flavored drink.	Both groups experienced paresthesia. Timing, intensity and localisation of symptoms were different between the groups, with asians reporting a slower onset of paresthesia related symptoms, and of lesser severity than caucasians.
Mor et al. (2018) (100)	To investigate the influence of acute BA intake on blood gas responses.	Male soccer players aged 19 - 24 yrs (BA n = 9, PLA n = 9)	3g dose, with 250ml of water.	No side-effect information provided.
Stautemas et al. (2018) (101)	To investigate blood BA pharmacokinetics of a single BA dose supplemented as either a fixed, or a weight-relative dose.	Male (19) and female (15) healthy omnivores, aged 25.1 ± 4.29 yrs (BA n = 34, with all 35 consuming the weight relative, and 28 consuming the fixed dose.	1.4 g (fixed dose, n = 34) or $10 mg \cdot kg^{-1} day^{-1}$.	None of the participants experienced paresthesia when consuming the weight-relative dose. Two reported paresthesia when consuming the fixed dose, and the moment of occurrrence matched their individual Cmax.

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Supplemental Table 3: Evidence from animal studies

Author (date)	Aim	Animal	BA Dose	Primary Outcome
Abebe et al. (2003a) (102)	To examine the effects of chronic BA induced taurine deficiency on the reactivity of the rat aorta to adenosine receptor simulation.	10 week old male Wistar - Kyoto rats.	3% BA in drinking water for 3 weeks.	Endogenous BA induced taurine deficiency caused differential inhibitory effects on adenosine receptor mediated vasorelaxation, indicating a taurine mediated modulation of blood flow regulation.
Abebe et al. (2003b) (103)	To examine the effects of chronic BA induced taurine deficiency on vascular reactivity.	10 week old male Wistar - Kyoto rats.	3% BA in drinking water for 3 weeks.	BA induced taurine depletion caused enhanced contractile responsiveness but depressed relaxation of the rat aorta.
Allo et al. (1997) (104)	To examine the effect of BA induced taurine deficiency on cellular necrosis in a regional model of ischemia.	Male Wistar rats weighing 250 - 300g.	3% BA in drinking water for 45 - 28 days.	BA induced taurine depletion resulted in a cardioprotective effect.
Bhattacharya et al. (2015) (105)	To investigate the effects of EGCG, BA and wheel running alone or in combination on several outcomes related to physical fitness, neuronal plasticity and cognition.	117 day old Male BALB/cJ mice.	581.5 ± 4.94 mg.kg.day-1 for 39 days.	BA did not influence physical fitness, adult hippocampal neurogenesis, or learning and memory measures, whereas exercise had robust effect on all of these outcomes. BA supplementation resulted in a reduction of body fat assessed by MRI.
Blancquaert et al. (2016) (106)	To investigate if BA is degraded by the transaminase enzymes GABA-T and ACXT2, and if this reaction regulates tissue HCD homeostasis.	Male C57BL/6 mice, sacrificed at 80 days.	0.1, 0.6 or 1.2% BA in drinking water for 14 days. Animals in the 0.1% group were further divided into subgroups based on daily s.c. injections with BA transaminase inhibitors (vigabatrin or AOA).	Skeletal muscle carnosine content is controlled by circulating BA levels, which can be suppressed by hepatic and renal BA transamination upon oral BA intake.
Choi et al. (2009) (107)	To determine if BA supplementation influences the hepatoxicity of CCI4.	Male ICR mice, weighing 20 - 25g.	3% in drinking water before CCI4 treatment.	BA had a hepatoprotective effect against CCI4, which may be acounted for by the increased supply of cysteine for production of taurine and/or GSH, both known to have important roles in the maintenance of usual hepatic physiology.
Dawson et al. (2002) (108)	To examine the influence of taurine supplementation and BA induced taurine depletion on indices of oxidative damage in a model of exercise induced muscle injury.	Male Sprague-Dawley rats weighing 180 - 200g	3% BA in drinking water for 4 weeks.	Both BA and taurine supplementation conferred a degree of oxidative protection against exercise induced muscle injury.
Ericson et al. (2011) (109)	To investigate the effect of ethanol administration on dopamine output in	Male Wistar rats..	5% BA in drinking water for 5 weeks.	BA induced taurine depletion did not prevent ethanol from increasing extracellular taurine when perfused in the

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	rats with BA induced taurine depletion.			nucleus accumbens.
Erman et al. (2004) (110)	To investigate the effect of BA induced taurine depletion on liver fibrosis in an ethandol-CCI4 induced cirrhosis model.	Wistar rats weighing 180 - 220g.	3% BA in drinking water for 4 weeks.	The BA group had normal liver structure, but rare monunclear cells in the portal area were present and ethanol and CCI4 treated rats proceeded to complete cirrhosis.
Everaert et al. (2013) (111)	To investigate the effect of BA and carnosine supplementation on muscle contractility	Naval medical research institute (NMRI) mice weighing 44.6 ± 6.4g.	0.6 or 1.2% BA in drinking water for 8 - 12 weeks.	BA supplementation (1.2% only) results in a leftward shift in the force-frequency relationship in EDL, and reduced fatigability in the soleus during isolated muscle contractions.
Everaert et al. (2013)(112)	To investigate the effect of BA supplementation on transcriptional events of genes related to HCD metabolism.	Male NMRI mice weighing 45.9 ± 5.9g.	1.2% BA in drinking water for 8 weeks.	CNDP2, TauTm and ABAT mRNA levels were higher and CARNS mRNA tended to be higher following supplementation. PAT1, PHT2 and HDC expression were not affected by BA supplementation.
Garcia-Ayuso et al. (2018) (113)	To examine the influence of BA induced taurine depletion on the retinal neuron response to light exposure.	Two month old albine Sprague Dawley female rats (150 - 180g)	3% BA in drinking water for 2months.	BA induced taurine deficiency resulted in retinal degradation, which was exacerbated by light exposure.
Gonzales-Quevedo et al. (2003) (114)	To investigate the effect of BA induced taurine depletion on biochemical changes induced by chronic exposure to low doses of methanol.	Male Sprague-Dawley rats weighing 154 ± 23g.	5% BA in drinking water for 2 weeks, followed by 3% for a further 4 weeks.	BA supplementation decreased taurine i in the plasma, hippocampus and posterior cortex, but not in the retina and optic nerve, with subsequent impact on glycinergic activity and aspartate metabolism.
Harada et al. (1990) (115)	To investigate the effects of BA induced taurine deficiency on cardiac calcium metabolism and redox mechanisms following doxorubicin administration.	Male Wistar rats..	3% BA in drinking water for 3 - 4 weeks.	Taurine deficiency *per se* did not impact cardiac calcium levels, but increased doxorubicin induced calcium accumulation, which may have resulted from an inhibition of ATP-dependent CA2+ uptake in isolated cardiac sarcolemmal vesicles. Taurine deficiency did not increase MDA content, but enhanced the doxorubicin mediated increase in myocardial MDA levels.
Hoffman et al. (2015) (116)	To investigate the effect of BA supplementation on PTSD like behavioural changes in rodents exposed to a predator scent stress.	Male Sprague-Dawley rats weighing 200 - 250g.	80 mg.kgBM-1 for 30 days.	BA supplementation attenuated some, but not all of the behaviours associated with PSS, which may have been related to an increase in brain carnosine and a subsequent protection of hippocampal BDNF expression.
Hoffman et al. (2017) (117)	To investigate the effect of BA supplementation on behavioural, cognitive and biochemical responses	Male Sprague-Dawley rats weighing 200 -	80 mg.kgBM-1 for 30 days.	The BA treated rats has a reduced incidence of mTBI, along with a reduced inflammatory response and higher hippocampal BDNF expression following blast exposure.

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	to mTBI and PTSH in rats exposed to a low-intensity blast wave.	250g.		
Horvath et al. (2016) (118)	To investigate the effect of BA induced taurine deficiency on muscle contractility and fatigue in wild-type and mdx mice.	C57BL/10 wild type and mdx mice aged 4.5 months.	3% BA in drinking water for 4 weeks.	BA supplementation enhanced fatigue resistance in both the WT and the mdx fast-twitch muscle.
Ideishi et al. (1994) (119)	To determine if BA induced taurine deficiency reduces blood pressure by stimulating the renal kallikrein-kinin system.	Male Dahl S rats aged 4 - 16 weeks.	2% BA in drinking water, along with a high-salt (8%) diet for 4 weeks.	Taurine appears to be an effective antihypertensive agent for salt-induced hypertension, which may involve the activation of renal kallikrein.
Jin et al. (2005) (120)	To investigate the effect of BA induced taurine deficiency on seizure activity, neuronal cell death and transporter expression during kainic acid induced epilepsy.	Male sprague-dawley rats weighing 140 - 160g.	3% BA in drinking water for 10 days.	BA induced taurine deficient rats were more susceptible to KA-induced epilepsy.
Kaczmarek et al. (2016) (121)	To investigate the effect of BA supplementation on contractile function in fast and slow motor units.	Adult male Wistar rats aged 6 months.	1% BA in drinking water for 10 weeks.	BA supplementation induced a number of contractile adaptations, along with enhanced fatigue resistance.
Kerai et al. (2001) (122)	To investigate the effect of BA induced taurine depletion on the pathological and biochemical lesions induced by alcohol.	Female sprague dawley rats weighing 125 - 150g	3% BA in drinking waer for 2 days (BA group n = 12), followed by the co-administration of alchohol and BA for a further 28 days.	BA supplementation increased the hepatoxicity of ethanol.
Kim et al. (2002) (123)	To investigate the effect of BA induced taurine depletion on lipolysaccharide inducted hepatoxicity.	Male Sprague-Dawley rats weighting 230 - 280 g.	3% BA in drinking water for 7 days prior to LPS challenge.	BA induced hepatic taurine depletion did not affect the hepatoxic outcome measures in this study. AST decreased in response to BA treatment.
Lake et al. (1988) (124)	To investigate if oral or injected BA depletes heart or retinal taurine.	Male sprague dawley rats weighing 250 - 270 g.	3% BA in drinking water, with animals analysed after 1, 2 and 3 weeks of treatment.	Oral BA treatment showed weight gain in comparison to controls. Oral BA treatment led to a significant reduction of heart taurine after 1, 2 and 3 weeks. The magnitude of treatment was less after 3 weeks, and by 6 weeks the BA group were not different to controls. Retinal taurine content was not different.
Lee et al. (2007) (125)	To investigate the effect of BA induced taurine deficiency on CCI4 induced acute hepatotoxicity.	Male ICR mice weighing 20 - 25g.	3% in drinking water for 1 week.	BA protected against CCI4 induced hepatotoxicity, potentially through increased cysteine availability.
Lilequist et al. (1982)	To examine the influence of BA and LA on the exploratory activity of	Spontaneously hypertensive	1% in drinking water for 7 days.	BA treatment inhibited the exploratory activity of the spontaneously hypertensive, but not the normostensive rats.

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(126)	spontaneoulsy hypertensive and normotensive rats.	(SHR) or normotensive Wistar Kyoto rats (WKR)aged 3 months.		
Liu et al. (2012) (127)	To investigate the molecular and neural mechanisms of itch and tingling induced by BA ingestion.	MgrgprD knockout or WT mice aged 2 - 3 months.	40mg.ml-1 of BA in a vehicle of 5% sucrose in water.	Comparison of response in MrgpgD knockout versus WT mice showed that BA directly induces itch in an MrgrprD dependent manner.
Lu et al. (1996) (128)	To investigate the effect of BA supplementation on the brain in taurine depleted and replete cats.	Female domestic cats who were fed on a taurine free, or 0.05% taurine diet for at least 2 years prior to the study.	5 cats in each group (taurine depleted or replete) were fed 5% BA in drinking water for 20 weeks.	BA supplementation caused a similar reduction of taurine in both groups of cats, but more BA accumulated in the brains of the taurine deprived compared to the taurine replete cats. The cerebellum of cats treated with BA had a number of pathological changes compared to non-BA treated cats. These neurotoxic changes appeared to be related to BA accumulation rather than taurine deficiency.
McBroom et al. (1996) (129)	To investigate mechanisms through which taurine may disrupt the ability to deal with a saline load.	Male and female adult Wistar rats (> 150g)	0.1 or 0.2M BA, with and without the co-ingestion of saline and taurine.	Taurine intake induced hypernatremia and appeared to interfere with normal homeostatic control mechanism, so exacerbating the hypernatremic response to saline ingestion and 3 of the 12 rats in this group died. BA ingestion counteracted this effect.
Mei et al. (1998) (130)	To determine if dietary histidine and BA supplementation increase HCD content and oxidative stability of pork muscle.	Hampshire-Yorkshire crossbred pigs, initially averaging 65kg body weight.	0.225% BA or o.225 + 0.4% histidine.	BA supplementation did not consistently increase or dramatically increase the oxidative stability of muscle which had been cooked or salted.
Miyaji et al. (2012) (131)	To investigate the tissue distribution of ATPGD1 mRNA and ATPGD1 and CN1 expression profiles in reponse to carnosine or BA administration.	Male SPF-bred ddY mice, weighing 34 g.	Mice were orally provided 2g.kg-1 of BA, then sacrificed after 15, 30, 60, 120, 180 or 360 mins of treatment.	ATPGD1 mRNA level increased at 1 and 3 hours post BA administration.
Mozaffari et al. (1986) (132)	To investigate the effect of BA induced taurine deficiency on myocardial contracility and carbohydrate metabolism.	Male Wistar rats, weighing 240 - 260g.	3% BA in drinking water for 3 weeks.	BA treatment did not impact myocardial contraction, but did stimulate an increased glycolytic rate and lactate production.
Mozaffari et al. (1997)	To investigate if BA induced taurine depletion affects renal excretory	6-week old male WKY rats.	3% BA in drinking water for 3 weeks.	Renal extraction of fluid and sodium after exposure to the saline load was lower in the BA treated group. Short term

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(133)	responses induced by the administration of a saline load.			BA treatment (2 days) increased sodium excretion without altering fluid excretion.
Mozaffari et al. (1998) (134)	To investigate the effect of BA induced taurine deficiency on renal excretory responses to hypotonic and hypertonic saline infusion.	7 week old male Wistar Kyoto rats.	3% BA in drinking water for 3 weeks.	BA induced taurine depletion altered the natriuretic and diuretic responses of the kidney to a hypotonic, but not hypertonic saline solution.
Mozaffari et al. (2000) (135)	To investigate the effect of BA induced taurine depletion on the cardiovascular response to vasoactive agents.	7 week old male Wistar-Kyoto rats.	3% BA in drinking water for 3 weeks.	BA induced taurine depletion does not impair baroreflex function, but does reduce pressor, but not heart-rate response to systemic administration of angiotensin II.
Mozaffari et al. (2006) (136)	To invesigate if BA induced taurine deficiency impacts renal and blood pressure responses to the loss of one kidney and/or dietary NaCL excess.	Male Wistar-Kyoto rats aged 7 - 8 weeks.	3% in drinking water for 2 weeks.	BA induced taurine deficiency modulates renal adaptation to combined uninephrectomy and dietart NaCL excess, resuling in an accelerated development of hypertension.
Murakami et al. (2010) (137)	To investigate if a taurine or beta-alanine supplementation impacts stress response.	Male ICR mice aged 3 weeks.	22.5mmol/kg-1 BA in a powder diet for approximately 4 weeks.	BA treatment resulted in anxiolytic-like effects as evidenced by improved performance in the elevated plus-maze test. This may have been mediated through altered hypothalamic 5-HIAA and hippocampal BDNF concentrations.
Naderi et al. (2016) (138)	To investigate the influence of BA supplementation on muscle carnosine and exercise induced lactate production.	Male wistar rats aged 2 months.	1.8% BA in drinking water for 4 weeks.	BA supplementation increased muscle carnosine and reduced serum lactate.
Naderi et al. (2017) (139)	To determine if glucose feeding during BA supplementation would enhance muscle carnosine concentration.	Male Wistar rats..	1.8% BA or 1.8% BA + 5% glucose in drinking water for 4 weeks.	Both BA groups increased muscle carnosine content, but the co-ingestion of BA and glucose did not have any additive effects.
Pansani et al. (2012) (140)	To investigate the influence of BA induced taurine deficiency on cardiac structure, function and metabolism.	Male wistar rats weighing 100g	3% BA in drinking water for 30 days.	BA induced taurine deficiency resulted in cardiac atrophy, as indicated by thinning of the ventricular wall, reduced left ventricular dry weight, decreated myocyte cross-sectional area and increased oxidative stress.
Parildar et al. (2007) (141)	To investigate the effect of BA induced taurine depletion on endogenous and induced lipid peroxidation levels in liver, brain, heart and erythrocytes and on hepatic pro and anti-oxidant balance.	Male Wistar rats weighing 180 - 200g	3% BA in drinking water for 1 month.	BA induced taurine depletion did not impact any of the assessed oxidative or anti-oxidative indicators.
Parildar et al.	To investigate the effect of BA	Young (5mo) and	3% BA in drinking water for 6	AA and NADPH induced peroxidation was increased in the

Supplementary Data

(2008) (142)	induced taurine depletion on lipid peroxidation potential and the antioxidant system of aged rats.	old (22mo) male Wistar rats	weeks.	hearts of aged rats following BA treatment.
Qi et al. (2018) (143)	To examine the effect of BA supplementation on growth performance, meat quality, antioxidant ability, carnosine content and carnosine related gene activity in broiler chicks.	1 day old Arbor Acres broilers.	250, 500, 1000 or 2000 mg/kg feed for 42 days.	Dietary BA intake improved growth performance, carnosine content, ameliorated antioxidant capacity and meat quality and upregulated the gene expression of carnosine synthesis related enzymes.
Saad et al. (2002) (144)	To investigate the effect of BA induced taurine depletion on the degree of CDDP-induced nephrotoxicity.	Male Wistar rats weighing 150 - 200g	3% BA in drinking water for 1 week.	BA induced taurine depletion resulted in increased serum creatinine, BUN and kidney mDA production in comparision with controls.
Seabra et al. (1997) (145)	To investigate the effect of BA induced taurine depletion on methylene dianiline induced hepatotoxicity.	Male sprague-dawley rats weighing 130 - 270g	3% in drinking water for 7 days.	BA induced taurine depletion increased DAPM toxicity.
Stegen et al. (2015) (146)	To investigate whether the metabolic protection afforded by carnosine occurs at the tissue or plasma level.	3 week old male sprague-dawley rats	1% BA in drinking water for 8 weeks.	Plasma, but not muscle carnosine is is involved in preventing early-stage lipoxidation in the circulation and inflammatory signaling in the muscle of rats.
Sturman et al. (1996) (147)	To investigate the effect of BA intake on taurine levels in cats.	Female domestic cats	5% BA in drinking water	BA intake reduced the taurine content of both taurine supplemented and taurine deprived cats. BA appeared to induce a neurotoxic effect in cats.
Vallejo et al. (2016) (148)	To investigate the independent and combined influence of HMB and BA supplementation on muscle contractility in a pre-clinical model of sarcopenia.	Male C57BL/6NTac mice sacrificed at 19 months old.	Purified diet containing 411 mg.kg-1BW BA for 8 weeks (BA group n = 12)	BA treatment increased absolute EDL twitch force, maximal tetanic force and the rate of force development.
Waterfield et al. (1993) (149)	To investigate the effect of BA induced hepatic taurine depletion on CCI4 induced hepatotoxicity.	Male Sprague-Dawlet rats, weighing 270 - 320 g.	3% BA in drinking water for 6 days.	BA treatment increased the hepatotoxicity of single CCI4 doses.
Yang et al. (2010) (150)	To investigate the effects of taurine supplementation and BA induced taurine depletion on reproductive indicators.	Wistar rats of different ages.	1% BA in drinking water for 22 days.	BA treatment reduced reproductive hormone level and reduced semen quality in aged rats.
Zhang et al.	To investigate the effect of BA	Rats	3% BA in drinking water for 5	BA treated rats had increased chemiluminescence

Supplementary Data

(1998) (151)	induced taurine depletion on lung macrophages.		weeks.	production in the macrophages isolated from the lungs, but no change to superoxide dismutase activity.

SUPPLEMENTAL REFERENCES

1. Al-horani RA. Effect of Seven Days of Beta-Alanine Supplementation on Cycle Ergometer Wingate Test Performance. Int J Coach Sci. 2017;11(2):45–59.

2. Allman B, Biwer A, Maitland C, DiFabio B, Coughlin E, Smith-Ryan A, Orsmbee MJ. The effect of short term beta alanine supplementation on physical performance and quality of life in Parkinson's Disease: A pilot study. J Exerc Physiol online. 2018;21(1):1–13.

3. Baguet A, Reyngoudt H, Pottier A, Everaert I, Callens S, Achten E, Derave W. Carnosine loading and washout in human skeletal muscles. J Appl Physiol. 2009;106(3):837–42.

4. Baguet A, Bourgois J, Vanhee L, Achten E, Derave W. Important role of muscle carnosine in rowing performance. J Appl Physiol. 2010;109(4):1096–101.

5. 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.

6. Bailey CH, Signorile JF, Perry AC, Jacobs KA, Myers ND. Beta-alanine does not enhance the effects of resistance training in older adults. J Diet Suppl. 2018;15(6):860–70.

7. Bassinello D, de Salles Painelli V, Dolan E, Lixandrão M, Cajueiro M, de Capitani M, Saunders B, Sale C, Artioli GG, Gualano B et al. Beta-alanine supplementation improves isometric, but not isotonic or isokinetic strength endurance in recreationally strength-trained young men. Amino Acids. 2018;1–11.

8. Bech S, Nielsen T, Hald M, Jakobsen J, Nordsborg N. No effect of β-alanine on muscle function and kayak performance. Med Sci Sports Exerc. 2018;50(3):562–9.

9. Bellinger PM, Minahan CL. Additive benefits of β-alanine supplementation and sprint-interval training. Med Sci Sports Exerc. 2016. 48(12): 2417-2425.

10. 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.

11. Bellinger PM, Minahan CL. The effect of β-alanine supplementation on cycling time trials of different length. Eur J Sport Sci. 2016;16(7):829–36.

12. Bellinger P, Howe S, Shing C. Effect of combined beta-alanine and sodiumbicarbonate supplementation on cycling performance. Med Sci Sport Exerc. 2012;44(8):1545–51.

13. Belviranli M, Okudan N, Revan S, Balci S, Gokbel H. Repeated supramaximal exercise-induced oxidative stress: Effect of beta-alanine plus creatine supplementation. Asian J Sports Med. 2016;7(1):1–7.

14. Bex T, Chung W, Baguet A, Stegen S, Stautemas J, Achten E, Derave W. Muscle carnosine loading by beta-alanine supplementation is more pronounced in trained vs. untrained muscles. J Appl Physiol. 2014;116(2):204–9.

15. Bex T, Chung W, Baguet A, Achten E, Derave W. Exercise training and beta-alanine-induced muscle carnosine loading. Front Nutr. 2015;7(2):13.

16. Black MI, Jones AM, Morgan PT, Bailey SJ, Fulford J, Vanhatalo A. The effects of β-alanine supplementation on muscle pH and the power-duration relationship during high-intensity exercise. Front Physiol. 2018;9:1–13.

17. Blancquaert L, Everaert I, Missinne M, Baguet A, Stegen S, Volkaert A, Petrovic M, Vervaet C, Achten E, De Maeyer M et al. Effects of histidine and β-alanine supplementation on human muscle carnosine storage. Med Sci Sport Exerc. 2017;49(3):602–9.

18. Brisola G, Artioli GG, Papoti M, Zagatto AM. Effects of four weeks of β-alanine supplementation on repeated sprint ability in water polo players. PLoS One. 2016;11(12):1–13.

19. Brisola G, de Souza Malta E, Santiago P, Vieira L, Zagatto A. Four weeks of b-alanine supplementation improves high-intensity game activities in water polo. Int J Physiol Perform. 2018;1–10.

20. Carpentier A, Olbrechts N, Vieillevoye S, Poortmans JR. β-Alanine supplementation slightly enhances repeated plyometric performance after high-intensity training in humans. Amino Acids.2015;47(7):1479–83.

21. Caruso J, Barbosa A, Perry R, Edwards R, Erickson L, Potter W, Wade Keller M. β-Alanine's impact on exercise and blood lactate values incurred from repetitive supramaximal activity. Isokinet Exerc Sci. 2014;22(4):303–9.

22. Carvalho VH, Oliveira AHS, de Oliveira LF, da Silva RP, Di Mascio P, Gualano B, Artioli GG, Medeiros MHG. Exercise and β-alanine supplementation on carnosine-acrolein adduct in skeletal muscle. Redox Biol. 2018;18:222–8.

23. Chung W, Shaw G, Anderson ME, Pyne DB, Saunders PU, Bishop DJ, Burke L. Effect of 10 week beta-alanine supplementation on competition and training performance in elite swimmers. Nutrients. 2012;4(10):1441–53.

24. Chung W, Baguet A, Bex T, Bishop DJ, Derave W. Doubling of muscle carnosine concentration does not improve laboratory 1-Hr cycling time-trial performance. Int J Sport Nutr Exerc Metab. 2014;24(3):315–24.

25. Church D, Hoffman J, Varanoske A, Wang R, Baker K, La Monica M, Beyer KS, Dodd SJ, Oliveira LP, Harris RC et al. Comparison of two β-alanine dosing protocols on muscle carnosine elevations. J Am Coll Nutr. 2017;36(8):608–16.

26. Claus G, Redkva P, Brisola G, Malta E, de Araujo Bonetti de Poli R, Miyagi W, Zagatto AM. Beta-alanine supplementation improves throwing velocities in repeated sprint ability and 200-m swimming performance in young water polo players. Pediatr Exerc Sci. 2017;29(2):203–12.

27. Cochran AJ, Percival ME, Thompson S, Gillen JB, MacInnis MJ, Potter MA, Tarnapolsky MA, Gibala MJ. Beta-alanine supplementation does not augment the skeletal muscle adaptive response to six weeks of sprint interval training. Int J Sport Nutr Exerc Metab. 2015;541–9.

28. Da Silva RP, de Oliveira LF, Saunders B, de Andrade Kratz C, de Salles Painelli V, da Eira Silva V, Marins JCB, Franchini E, Gualano B, Artioli GG. Effects of β-alanine and sodium bicarbonate supplementation on the estimated energy system contribution during high-intensity intermittent exercise. Amino Acids. doi. 10.1007/s00726-018-2643-2

29. Danaher J, Gerber T, Wellard RM, Stathis CG. The effect of β-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.

30. Del Favero S, Roschel H, Solis MY, Hayashi AP, Artioli GG, Otaduy MC, Benatti FB, Harris RC, Wise JA, Leite CC et al. Beta-alanine (Carnosyn^{TM}) supplementation in elderly subjects (60-80 years): Effects on muscle carnosine content and physical capacity. Amino Acids. 2012;43(1):49–56.

31. Derave W, Ozdemir MS, Harris RC, Pottier A, Reyngoudt H, Koppo K, Wise JA, Achten E. Beta-alanine supplementation augments muscle carnosine content and attenuates fatigue during repeated isokinetic contraction bouts in trained sprinters. J Appl Physiol. 2007;103(5):1736–43.

32. Donovan T, Ballam T, Morton JP, Close GL. B-alanine improves punch force and frequency in amateur boxers during a simulated contest. Int J Sport Nutr Exerc Metab. 2012;22(5):331–7.

33. Ducker KJ, Dawson B, Wallman KE. Effect of beta-alanine supplementation on 800-m running performance. Int J Sport Nutr Exerc Metab. 2013;23(6):554–61.

34. Ducker K, Dawson B, Wallman K. Effect of beta alanine and sodium bicarbonate supplementation on repeated-sprint performance. J Strength Cond Res. 2013;27(12):3450–60.

35. Ducker KJ, Dawson B, Wallman KE. Effect of beta-alanine supplementation on 2,000-m rowing-

ergometer performance. 2013;(2012):336–43.

36. Ghiasvand R, Askari G, Malekzadeh J, Hajishafiee M, Daneshvar P, Akbari F. Effects of six weeks of beta-alanine administration on VO_2 max, time to exhaustion and lactate concentrations in physical education students. Int J Prev Med. 2012;3(8):559–63.

37. Eilaki AA, Afzalpour ME, Bagheri R, Ziaaldini MM. The effect of beta-alanine supplementation on first and second ventilatory threshold of male swimmers. Nutr Food Sci Res. 2018;5(3):9–14.

38. Furst T, Massaro A, Miller C, Williams BT, LaMacchia ZM, Horvath PJ. β-Alanine supplementation increased physical performance and improved executive function following endurance exercise in middle aged individuals. J Int Soc Sports Nutr. 2018;15(1):1–8.

39. Glenn JM, Gray M, Stewart R, Moyen NE, Kavouras SA, Dibrezzo R, Turner R, Baum J. 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.

40. Greer BK, Katalinas ME, Shaholli DM, Gallo PM. Beta-alanine supplementation fails to increase peak aerobic power or ventilatory threshold in aerobically trained males. J Diet Suppl. 2016;13(2):165–70.

41. Gross M, Bieri K, Hoppeler H, Norman B, Vogt M, Gross M. Beta-alanine supplementation improves jumping power and affects severe - intensity performance in professional alpine skiers. 2014;05:1–23.

42. Gross M, Boesch C, Bolliger CS, Norman B, Gustafsson T, Hoppeler H, Vogt M. Effects of beta-alanine supplementation and interval training on physiological determinants of severe exercise performance. Eur J Appl Physiol. 2014;114(2):221–34.

43. 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. 2015;118(5):604–12.

44. Harris RC, Tallon MJ, Dunnett M, Boobis L, Coakley J, Kim HJ, Fallowfield JL, Hill CA, Sale C, Wise JA. The absorption of orally supplied β-alanine and its effect on muscle carnosine synthesis in human vastus lateralis. Amino Acids. 2006;30(3):279–89.

45. Hill CA, Harris RC, Kim HJ, Harris BD, Sale C, Boobis LH, Kim CK, Wise JA. Influence of β-alanine supplementation on skeletal muscle carnosine concentrations and high intensity cycling capacity. Amino Acids. 2007;32(2):225–33.

46. Hobson RM, Harris RC, Martin D, Smith P, Macklin B, Gualano B, Sale C. Effect of beta-alanine with and without sodium bicarbonate on 2,000-m rowing performance. Int J Sport Nutr Exerc Metab. 2013; 23(5):480–7.

47. James RM, Cooper SB, Robertson J, Martin D, Harris RC, Sale C. Effect of b-alanine supplementation on 20 km cycling time trial performance. Rev Bras Educ Física e Esporte. 2014;28(3):395–403.

48. Hoffman J, Ratamess N, Ross R, Kang J, Magrelli J, Neese K, Faigenbaum AD, Wise JA. β-alanine and the hormonal response to exercise. Int J Sports Med. 2008;29(12):952–8.

49. Hoffman JR, Ratamess NA, Faigenbaum AD, Ross R, Kang J, Stout JR, Wise JA. 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.

50. Hoffman JR, Landau G, Stout JR, Dabora M, Moran DS, Sharvit N, Hoffman MW, Moshe YB, McCormack WP, Hirschhorn G et al. B-alanine supplementation improves tactical performance but not cognitive function in combat soldiers. J Int Soc Sports Nutr. 2014;11(1):15.

51. Hoffman JR, Landau G, Stout JR, Hoffman MW, Shavit N, Rosen P, Moran DS, Fukuda DH, Shelef I, Carmom E et al. Beta-alanine ingestion increases muscle carnosine content and combat specific performance in soldiers. Amino Acids. 2015;47(3):627–36.

52. Hoffman J, Gepner Y, Hoffman M, Zelicha H, Shapira S, Ostfeld I. Effect of high-dose, short-duration

b-alanine supplementatin on circulating IL-10 concentrations during intense military training. J Strength Cond Res. 2018; 32(10): 2978-2981.

53. Howe ST, Bellinger PM, Driller MW, Shing CM, Fell JW. The effect of β-alanine supplementation on isokinetic force and cycling performance in highly-trained cyclists. Int J Sport Nutr Exerc Metab. 2013; 23(6): 562-70.

54. Jagim A, Wright G, Glenn Brice A, Doberstein ST. Effects of beta-alanine supplementation on sprint endurance. J Strength Cond Res. 2013;27(2):526–32.

55. Jones RL, Barnett CT, Davidson J, Maritza B, Fraser WD, Harris R, Sale C. B-alanine supplementation improves in-vivo fresh and fatigued skeletal muscle relaxation speed. Eur J Appl Physiol. 2017;117(5):867–79.

56. Jordan T, Lukaszuk J, Misic M, Umoren J. Effect of beta-alanine supplementation on the onset of blood lactate accumulation (OBLA) during treadmill running. J Int Soc Sports Nutr. 2010;7(1):20.

57. Kendrick IP, Harris RC, Kim HJ, Kim CK, Dang VH, Lam TQ, Bui TT, Smith M, Wise JA. The effects of 10 weeks of resistance training combined with beta-alanine supplementation on whole body strength, force production, muscular endurance and body composition. Amino Acids. 2008;34(4):547–54.

58. Kendrick IP, Kim HJ, Harris RC, Kim CK, Dang VH, Lam TQ, Bui TT, Wise JA. The effect of 4 weeks beta-alanine supplementation and isokinetic training on carnosine concentrations in type I and II human skeletal muscle fibres. Eur J Appl Physiol. 2009;106(1):131–8.

59. Kern B, Robinson T. Effects of β-alanine supplementation on performance and body composition in collegiate wrestlers and football players. J Strength Cond Res. 2011;25(7):1804–15.

60. De Andrade Kratz C, de Salles Painelli V, de Andrade Nemezio KM, da Silva RP, Franchini E, Zagatto AM, Gualano B, Artioli GG. Beta-alanine supplementation enhances judo-related performance in highly-trained athletes. J Sci Med Sport. 2017;20(4):403–8.

61. Kresta JY, Oliver J, Jagim A, Kreider R, Fluckey J, Reichman S, Kelly K, Meininger C, Mertens-Talcott S, Rasmussen C, Kreider RB. Effects of 28 days of beta-alanine and creatine monohydrate supplementation on muscle carnosine, body composition and exercise performance in recreationally active females. J Int Soc Sports Nutr. 2014; 11(1): 55.

62. Maté-Muñoz JL, Lougedo JH, Garnacho-Castaño M V, Veiga-Herreros P, Del M, Lozano-Estevan C, Garcia-Fernandez P, de Jesus F, Guodemar-Perez J, San Juan AR, Dominguez R. Effects of β-alanine supplementation during a 5-week strength training program: A randomized, controlled study. J Int Soc Sports Nutr. 2018; 15: 19.

63. McCormack WP, Stout JR, Emerson NS, Scanlon TC, Warren AM, Wells AJ, Gonzales AM, Mangine GT, Robinson EH, Fragala MS et al. Oral nutritional supplement fortified with beta-alanine improves physical working capacity in older adults: A randomized, placebo-controlled study. Exp Gerontol. 2013;48(9):933–9.

64. Mero AA, Hirvonen P, Saarela J, Hulmi JJ, Hoffman JR, Stout JR. Effect of sodium bicarbonate and beta-alanine supplementation on maximal sprint swimming. J Int Soc Sports Nutr. 2013;10(1):52.

65. Milioni F, Redkva PE, Barbieri FA, Zagatto AM. Six weeks of β-alanine supplementation did not enhance repeated-sprint ability or technical performances in young elite basketball players. Nutr Health. 2017;23(2):111–8.

66. Outlaw J, Smith-Ryan A, Buckley A, Urbina S, Hayward S, Wingfield H, Campbell B, Foster C, Taylor LW, WIlborn CD. Effects of β-alanine on body composition and performance measures in collegiate women. J Strength Cond Res. 2016;30(9):2627–37.

67. De Salles Painelli V, Roschel H, de Jesus F, Sale C, Harris RC, Solis MY, Benatti FB, Gualano B, Lancha AH, Artioli GG. The ergogenic effect of beta-alanine combined with sodium bicarbonate on high-intensity swimming performance. Appl Physiol Nutr Metab. 2013;38(5):525–32.

68. De Salles Painelli V, Saunders B, Sale C, Harris RC, Solis MY, Roschel H, Gualano B, Artioli GG, Lancha AH. Influence of training status on high-intensity intermittent performance in response to β-alanine supplementation. Amino Acids. 2014;46(5):1207–15.

69. Rosas F, Ramírez-Campillo R, Martínez C, Caniuqueo A, Cañas-Jamet R, McCrudden E, Meyla C, Moran J, Nakamura FY, Pereira LA et al. Effects of plyometric training and beta-alanine supplementation on maximal-intensity exercise and endurance in female soccer players. J Hum Kinet. 2017;58(1):99–109.

70. Sale C, Saunders B, Hudson S, Wise J, Harris R, Sunderland C. Effect of β-alanine plus sodium bicarbonate on high-intensity cycling capacity. Med Sci Sport Exerc. 2011;43(10):1972–8.

71. Sale C, Hill CA, Ponte J, Harris RC. B-Alanine supplementation improves isometric endurance of the knee extensor muscles. J Int Soc Sports Nutr. 2012;9(1):26.

72. Santana JO, de Freitas MC, dos Santos DM, Rossi FE, Lira FS, Rosa-Neto JC, Caperuto EC. Beta-alanine supplementation improved 10-km running time trial in physically active adults. Front Physiol. 2018; doi: 10.3389/fphys.2018.01105/full.

73. Saunders B, Sale C, Harris RC, Sunderland C. Effect of beta-alanine supplementation on repeated sprint performance during the Loughborough Intermittent Shuttle Test. Amino Acids. 2012;43(1):39–47.

74. Saunders B, Sunderland C, Harris RC, Sale C. β-alanine supplementation improves YoYo intermittent recovery test performance. J Int Soc Sports Nutr. 2012;9(1):39.

75. Saunders B, Sale C, Harris RC, Sunderland C. Effect of sodium bicarbonate and β -alanine on repeated sprints during intermittent exercise performed in hypoxia. Int J Sport Nutr Exerc Metab. 2014;24:196–205.

76. Saunders B, Franchi M, de Oliveira L, da Eira Silva V, da Silva RP, de Salles Painelli V, et al. Chronic (24 weeks) β-alanine supplementation does not affect muscle taurine or blood clinical chemistry (Abstract). Med Sci Sports Exerc. 2018; 50: 590.

77. Smith AE, Moon JR, Kendall KL, Graef JL, Lockwood CM, Walter AA, Beck TW, Cramer JT, Stout JR. The effects of beta-alanine supplementation and high-intensity interval training on neuromuscular fatigue and muscle function. Eur J Appl Physiol. 2009;105(3):357–63.

78. Smith AE, Stout JR, Kendall KL, Fukuda DH, Cramer JT. Exercise-induced oxidative stress: The effects of β-alanine supplementation in women. Amino Acids. 2012;43(1):77–90.

79. Smith-Ryan A, Fukuda D, Stout J, Kendall K. High-velocity intermittent running: effects of beta-alanine supplementation. J Strength Cond Res. 2012;26(10):2798–805.

80. Smith-Ryan AE, Fukuda DH, Stout JR, Kendall KL. The influence of β-alanine supplementation on markers of exercise-induced oxidative stress. Appl Physiol Nutr Metab. 2014;39(1):38–46.

81. Smith-Ryan AE, Woessner MN, Melvin MN, Wingfield HL, Hackney AC. The effects of beta-alanine supplementation on physical working capacity at heart rate threshold. Clin Physiol Funct Imaging. 2014;34(5):397–404.

82. Solis MY, Cooper S, Hobson RM, Artioli GG, Otaduy MC, Roschel H, Robertson J, Martin F. Painelli V, Harris RC et al. Effects of beta-alanine supplementation on brain homocarnosine/carnosine signal and cognitive function: An exploratory study. PLoS One. 2015;10(4):1–16.

83. Stegen S, Blancquaert L, Everaert I, Bex T, Taes Y, Calders P, Achten E, Derave W. Meal and beta-alanine coingestion enhances muscle carnosine loading. Med Sci Sports Exerc. 2013;45(8):1478–85.

84. Stellingwerff T, Anwander H, Egger A, Buehler T, Kreis R, Decombaz J, Boesch C. Effect of two β-alanine dosing protocols on muscle carnosine synthesis and washout. Amino Acids. 2012;42(6):2461–72.

85. Stout J, Cramer J, Mielke M, O'Kroy J, Torok D, Zoeller R. Effects of twenty-eight days of beta-alanine

and creatine monohydrate supplementation on the physical working capacity at neuromuscular fatigue threshold. J Strength Cond Res. 2006;20(4):928–31.

86. Stout JR, Cramer JT, Zoeller RF, Torok D, Costa P, Hoffman JR, Harris RC, O'Kroy J. Effects of beta-alanine supplementation on the onset of neuromuscular fatigue and ventilatory threshold in women. Amino Acids. 2007;32(3):381–6.

87. Stout JR, Graves BS, Smith AE, Hartman MJ, Cramer JT, Beck TW, Harris RC. The effect of beta-alanine supplementation on neuromuscular fatigue in elderly (55–92 Years): A double-blind randomized study. J Int Soc Sports Nutr. 2008;5(1):21.

88. Sweeney K, Wright G, Glenn Brice A, Doberstein S. The effect of beta-alanine supplementation on power performance during repeated sprint activity. J Strength Cond Res. 2010;24(1):79–87.

89. Tobias G, Benatti FB, De Salles Painelli V, Roschel H, Gualano B, Sale C, Harris RC, Lancha AH, Artioli GG. Additive effects of beta-alanine and sodium bicarbonate on upper-body intermittent performance. Amino Acids. 2013;45(2):309–17.

90. Van Thienen R, Van Proeyen K, Eynde B Vanden, Puype J, Lefere T, Hespel P. β-Alanine improves sprint performance in endurance cycling. Med Sci Sports Exerc. 2009;41(4):898–903.

91. Varanoske A, Hoffman J, Church D, Wang R, Baker K, Dodd S, Coker NA, Oliveira LP, Dawson VL, Fukuda DH et al. Influence of skeletal muscle carnosine content on fatigue during repeated resistance exercise in recreationally active women. Nutrients. 2017;9(9):988.

92. Varanoske AN, Hoffman JR, Church DD, Coker NA, Baker KM, Dodd SJ, Harris RC, Oliveira LP, Dawson VL, Wang R et al. Comparison of sustained-release and rapid-release β-alanine formulations on changes in skeletal muscle carnosine and histidine content and isometric performance following a muscle-damaging protocol. Amino Acids. 2018; doi:10.1007/s00726-018-2609-4

93. Walter A, Smith A, Kendall K, Stout J, Cramer J. Six weeks of high-intensity interval training with and without beta-alanine supplementation for improving cardiovascular fitness in women. J Strength Cond Res. 2010;24(5):1199–207.

94. Zoeller RF, Stout JR, O'Kroy JA, Torok DJ, Mielke M. Effects of 28 days of beta-alanine and creatine monohydrate supplementation on aerobic power, ventilatory and lactate thresholds, and time to exhaustion. Amino Acids. 2007;33(3):505–10.

95. Bellinger PM, Minahan CL. Performance effects of acute β-alanine induced paresthesia in competitive cyclists. Eur J Sport Sci. 2016;16(1):88–95.

96. Décombaz J, Beaumont M, Vuichoud J, Bouisset F, Stellingwerff T. Effect of slow-release β-alanine tablets on absorption kinetics and paresthesia. Amino Acids. 2012;43(1):67–76.

97. Glenn J, Smith K, Moyen N, Binns A, Gray M. Effects of acute beta-alanine supplementation on anaerobic performance in trained female cyclists. J Nutr Sci Vitaminol (Tokyo). 2015;61(2):161–6.

98. Kelly V. β–alanine: Performance effects, usage and side effects (dissertation). University of Queensland: 104 - 119.

99. MacPhee S, Weaver I, Weaver D. An evaluation of interindividual responses to the orally administered neurotransmitter beta-Alanine. J Amino Acids. 2013;1–5.

100. Mor A, Ipekoglu G. The acute effects of beta-alanine on blood gas of athletes after maximal research. Res K of Pharm Biol Chem Sci. 2019; 9:4.

101. Stautemas J, Everaert I, Lefevere FBD, Derave W. Pharmacokinetics of β-alanine using different dosing strategies. Front Nutr. 2018; 5:70.

102. Abebe W, Mozaffari MS. Effect of taurine deficiency on adenosine receptor-mediated relaxation of the rat aorta. Vascul Pharmacol. 2003;40(4):219–28.

103. Abebe W, Mozaffari MS. Taurine depletion alters vascular reactivity in rats. Can J Physiol Pharmacol.

2003;81(9):903–9.

104. Allo S, Bagby L, Schaffer S. Taurine depletion, a novel mechanism for cardioprotection from regional ischemia. Am J Physiol. 1997;273(4):1956–61.

105. Bhattacharya T, Pence B, Ossyra J, Gibbons T, Perez S, McCusker R, Kelley KW, Johnson RW, Woods JA. Rhodes JS. Exercise but not (-)-epigallocatechin-3-gallate or β-alanine enhances physical fitness, brain plasticity, and behavioral performance in mice. Physiol Behav. 2015;145(29–37).

106. Blancquaert L, Baba SP, Kwiatkowski S, Stautemas J, Stegen S, Barbaresi S, Chung W, Boakye AA, Hoetker JD, Bhatnagar A et al. Carnosine and anserine homeostasis in skeletal muscle and heart is controlled by β-alanine transamination. J Physiol. 2016;594(17):4849–63.

107. Choi D, Kim S, Kwon D, Lee S, Kim Y. Taurine depletion by beta-alanine inhibits induction of hepatotoxicity in mice treated acutely with carbon tetrachloride. Adv Exp Med Biol. 2009;643:305–11.

108. Dawson R, Biasetti M, Messina S, Dominy J. The cytoprotective role of taurine in exercise-induced muscle injury. Amino Acids. 2002;22(4):309–24.

109. Ericson M, Chau P, Clark R, Adermark L, Soderpalm B. Rising taurine and ethanol concentrations in nucleus accumbens interact to produce dopamine release after ethanol administration. Addict Biol. 2011;16(3):377–85.

110. Erman F, Balkan J, Çevikbaş U, Koçak-Toker N, Uysal M. Betaine or taurine administration prevents fibrosis and lipid peroxidation induced by rat liver by ethanol plus carbon tetrachloride intoxication. Amino Acids. 2004;27(2):199–205.

111. Everaert I, De Naeyer H, Taes Y, Derave W. Gene expression of carnosine-related enzymes and transporters in skeletal muscle. Eur J Appl Physiol. 2013;113(5):1169–79.

112. Everaert I, Stegen S, Vanheel B, Taes Y, Derave W. Effect of beta-alanine and carnosine supplementation on muscle contractility in mice. Med Sci Sport Exerc. 2013;45(1):43–51.

113. García-Ayuso D, Pierdomenico J Di, Hadj-Said W, Marie M, Agudo-Barriuso M, Vidal-Sanz M, Picaud S, Villegas-Perez MP. Taurine depletion causes iprgc loss and increases light- induced photoreceptor dKaczegeneration. Investig Ophthalmol Vis Sci. 2018;59(3):1396–409.

114. González-Quevedo A, Obregón F, Urbina M, Roussó T, Lima L. Effects of taurine deficiency and chronic methanol administration on rat retina, optic nerve and brain amino acids and monoamines. Nutr Neurosci. 2003;6(4):253–61.

115. Harada H, Cusack BJ, Olson RD, Stroo W, Azuma J, Hamaguchi T, Schaffer SW. Taurine deficiency and doxorubicin: interaction with the cardiac sarcolemmal calcium pump. Biochem Pharmacol. 1990;39(4):745–51.

116. Hoffman JR, Ostfeld I, Stout JR, Harris RC, Kaplan Z, Cohen H. β-alanine supplemented diets enhance behavioral resilience to stress exposure in an animal model of PTSD. Amino Acids. 2015;47(6):1247–57.

117. Hoffman JR, Zuckerman A, Ram O, Sadot O, Stout JR, Ostfeld I, Cohen H. Behavioral and inflammatory response in animals exposed to a low-pressure blast wave and supplemented with β-alanine. Amino Acids. 2017;49(5):871–86.

118. Horvath DM, Murphy RM, Mollica JP, Hayes A, Goodman CA. The effect of taurine and β-alanine supplementation on taurine transporter protein and fatigue resistance in skeletal muscle from mdx mice. Amino Acids. 2016;48(11):2635–45.

119. Ideishi M, Miura S, Sakai T, Sasaguri M, Misumi Y, Arakawa K. Taurine amplifies renal kallikrein and prevents salt-induced hypertension in Dahl rats. J Hypertens. 1994;12(6):653–61.

120. Jin H-B, Li B, Gu J, Cheng J-S, Yang R. Electro-acupuncture improves epileptic seizures induced by kainic acid in taurine-depletion rats. Acupunct Electrother Res. 2005;30(3–4):207–17.

121. Kaczmarek D, Łochyński D, Everaert I, Pawlak M, Derave W, Celichowski J. Role of histidyl dipeptides in contractile function of fast and slow motor units in rat skeletal muscle. J Appl Physiol. 2016;121(1):164–72.

122. Kerai MD, Waterfield CJ, Kenyon SH, Asker DS, Timbrell JA. The effect of taurine depletion by beta-alanine treatment on the susceptibility to ethanol-induced hepatic dysfunction in rats. Alcohol Alcohol. 2001;36(1):29–38.

123. Kim SK, Kim YC. Attenuation of bacterial lipopolysaccharide-induced hepatotoxicity by betaine or taurine in rats. Food Chem Toxicol. 2002;40(4):545–9.

124. Lake N, De Marte L. Effects of beta-alanine treatment on the taurine and DNA content of the rat heart and retina. Neurochem Res. 1988;13(10):1003–6.

125. Lee SY, Kim YC. Effect of beta-alanine administration on carbon tetrachloride-induced acute hepatotoxicity. Amino Acids. 2007;33(3):543–6.

126. Lilequist R, Paasonen M, Solatunturi E. Beta-Alanine and alpha-L-alanine inhibit the exploratory activity of spontaneously hypertensive rats. Experientia. 1982;38(3):379–80.

127. Liu Q, Sikand P, Ma C, Tang Z, Han L, Li Z, Sun S, LaMotte RH, Dong X. Mechanisms of itch evoked by β-alanine. J Neurosci. 2012;32(42):14532–7.

128. Lu P, Xu W, Sturman JA. Dietary β-alanine results in taurine depletion and cerebellar damage in adult cats. J Neurosci Res. 1996;43(1):112–9.

129. McBroom M, Davidson N. Beta-alanine protects against taurine and NaCl--induced hypernatremia in the rat. Proc Soc Exp Biol Med. 1996;211(2):184–9.

130. Mei L, Cromwell GL, Crum AD, Decker EA. Influence of dietary beta-alanine and histidine on the oxidative stability of pork. Meat Sci. 1998;49(1):55–64.

131. Miyaji T, Sato M, Maemura H, Takahata Y, Morimatsu F. Expression profiles of carnosine synthesis-related genes in mice after ingestion of carnosine or ß-alanine. J Int Soc Sports Nutr. 2012;9:1–5.

132. Mozaffari MS, Tan BH, Lucia MA, Schaffer SW. Effect of drug-induced taurine depletion on cardiac contractility and metabolism. Biochem Pharmacol. 1986;35(6):985–9.

133. Mozaffari MS, Azuma J, Patel C, Schaffer SW. Renal excretory responses to saline load in the taurine-depleted and the taurine-supplemented rat. Biochem Pharmacol. 1997;54(5):619–24.

134. Mozaffari M, Warren B, Azuma J, Schaffer S. Renal excretory responses of taurine-depleted rats to hypotonic and hypertonic saline infusion. Amino Acids. 1998;15:109–16.

135. Mozaffari MS, Abebe W. Cardiovascular responses of the taurine-depleted rat to vasoactive agents. Amino Acids [Internet]. 2000;19(3–4):625–34.

136. Mozaffari MS, Patel C, Abdelsayed R, Schaffer SW. Accelerated NaCl-induced hypertension in taurine-deficient rat: Role of renal function. Kidney Int. 2006;70(2):329–37.

137. Murakami T, Furuse M. The impact of taurine-and beta-alanine-supplemented diets on behavioral and neurochemical parameters in mice: Antidepressant versus anxiolytic-like effects. Amino Acids. 2010;39(2):427–34.

138. Naderi A, Hemat Far A, Willems MET, Sadeghi M. Effect of four weeks of β-alanine supplementation on muscle carnosine and blood serum lactate during exercise in male rats. J Diet Suppl. 2016;13(5):487–94.

139. Naderi A, Sadeghi M, Sarshin A, Imanipour V, Nazeri SA, Farkhayi F, Willems ME. Muscle carnosine concentration with the co-ingestion of carbohydrate with β-alanine in male rats. J Diet Suppl. 2017;14(4):373–9.

140. Pansani MC, Azevedo PS, Rafacho BPM, Minicucci MF, Chiuso-Minicucci F, Zorzella-Pezavento SG,

Marchini JS, Padovan GJ, Fernandes AA, Matsubara BB et al. Atrophic cardiac remodeling induced by taurine deficiency in wistar rats. PLoS One. 2012;7(7):1–6.

141. Parildar-Karpuzoğlu H, Doğru-Abbasoğlu S, Balkan J, Aykaç-Toker G, Uysal M. Decreases in taurine levels induced by β-alanine treatment did not affect the susceptibility of tissues to lipid peroxidation. Amino Acids. 2007;32(1):115–9.

142. Parildar H, Dogru-Abbasoglu S, Mehmetçik G, Ozdemirler G, Koçak-Toker N, Uysal M. Lipid peroxidation potential and antioxidants in the heart tissue of beta-alanine- or taurine-treated old rats. J Nutr Sci Vitaminol (Tokyo). 2008;54(1):61–5.

143. Qi B, Wang J, Ma YB, Wu SG, Qi GH, Zhang HJ. Effect of dietary β-alanine supplementation on growth performance, meat quality, carnosine content, and gene expression of carnosine-related enzymes in broilers. Poult Sci. 2018;97(4):1220–8.

144. Saad SY, Al-Rikabi AC. Protection effects of taurine supplementation against cisplatin-induced nephrotoxicity in rats. Chemotherapy. 2002;48(1):42–8.

145. Seabra V, Timbrell JA. Modulation of taurine levels in the rat liver alters methylene dianiline hepatotoxicity. Toxicology. 1997;122(3):193–204.

146. Stegen S, Stegen B, Aldini G, Altomare A, Cannizzaro L, Orioli M, Gerlo S, Deldicque L, Ramaekers M, Hespel P et al. Plasma carnosine, but not muscle carnosine, attenurates high-fat diet-induced metabolic stress. Appl Physiol Nutr Metab. 2015; 40(9):868–76.

147. Sturman J, Messing J. Depletion of feline taurine levels by beta-alanine and dietary taurine restriction. Nutr Res. 1996;16(5):789–95.

148. Vallejo J, Spence M, Cheng AL, Brotto L, Edens NK, Garvey SM, Brotto M. Cellular and physiological effects of dietary supplementation with β-hydroxy-β- methylbutyrate (hmb) and β-alanine in late middle-aged mice. PLoS One. 2016;11(3).

149. Waterfield CJ, Turton JA, Scales MDC, Timbrell JA. Reduction of liver taurine in rats by beta-alanine treatment increases carbon-tetrachloride toxicity. Toxicology. 1993;77(1–2):7–20.

150. Yang J, Wu G, Feng Y, Lv Q, Lin S, Hu J. Effects of taurine on male reproduction in rats of different ages. J Biomed Sci. 2010; 24(17): S1-S9.

151. Zhang X, Lombardini J. Effects of in vivo taurine depletion on induced-chemiluminescence production in macrophages isolated from rat lungs. Amino Acids. 1998;15:179–86.