Low efficiency of β-alanine supplementation to increase muscle carnosine: a retrospective analysis from a 4-week trial

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Abstract

Supplementation with β-alanine (BA) increases muscle carnosine content, although the amount of BA used for muscle carnosine loading has been suggested to be low. However, methodological issues may have underestimated the amount of BA used. The aim of this study was to determine the estimated amount of BA converted to muscle carnosine, using a retrospective analysis from a 4-week randomized controlled trial investigating the effects of BA supplementation on muscle carnosine content of the m. vastus lateralis. Twenty-five males (age 27±5 years, height 1.74±0.09 m, body mass 77.4±11.5 kg) were supplemented with 6.4 g·day^{-1} of BA (N=17) or placebo (PL; N=8) for 28 days. Pre- and post-supplementation participants provided a muscle biopsy subsequently analysed for carnosine content using HPLC. Data were analysed using mixed-models and Pearson's correlations. Muscle carnosine content increased by +11.0±6.7 mmol·kg^{-1}dm (P<0.0001) in BA, with no change in PL (P=0.99). The estimated amount of BA converted to muscle carnosine was 2.1±1.2% (Range: 0.5 to 4.5%) of the total dose ingested. Pearson's correlations showed that pre-supplementation carnosine was correlated to post-supplementation carnosine in the BA group (r=0.65, r^2=0.38, P=0.009), but not the absolute change in carnosine (r=-0.28, r^2=0.08, P=0.28) or the amount of BA used (r=-0.31, r^2=0.10, P=0.22). The estimated amount of ingested BA used for carnosine synthesis was extremely low following 4 weeks of BA supplementation at 6.4 g·day^{-1}. Data suggest that very little of the BA ingested is used for muscle carnosine synthesis and highlights the potential for further work to optimise BA supplementation in humans.

Keywords: Carnosine Synthesis; Beta-Alanine Incorporation; Optimization; Supplementation Strategy; High-Performance Liquid Chromatography.

Introduction

Beta-alanine (BA) has rapidly become a popular supplement since Harris et al.[1] showed that supplementation at an average of 5.2 g·day^{-1} for 4 weeks could increase muscle carnosine content. Further investigations have confirmed the efficacy of 23 to 28 days of BA supplementation at doses between 3.2 and 6.4 g·day^{-1} to increase muscle carnosine[2-6]. It has also been consistently shown that BA supplementation, and subsequently increased muscle carnosine content, improve high-intensity exercise[7].

Overall whole body retention of BA has been shown to be high using both standard (~96%) and sustained-release (>99%) BA formulas[8], however, efficiency regarding the amount of BA used for muscle carnosine synthesis has been suggested to be low. Approximately 2.8% (range: 2.4–5.8%) of BA is incorporated into carnosine synthesis when assuming that 40% of body mass is muscle mass[9,10]. However, these calculations were based upon percentage changes in muscle carnosine concentration as measured by ^{1}H-MRS; using

percentage increases may misrepresent actual changes of carnosine in muscle, particularly in individuals with low initial content. Thus, it is recommended that any calculations be based upon absolute changes in muscle carnosine content. Furthermore, the small muscle groups (*m. deltoid, soleus* and *gastrocnemius*) analysed may have led to smaller increases in muscle carnosine content than in the *m. vastus lateralis*, which may have led to an underestimation of the amount of BA used in the subsequent calculations, particularly using percent changes measured by ^{1}H-MRS. Thus, determination of the amount of BA used for synthesis of muscle carnosine content using chromatographic (*i.e.*, HPLC) quantification of biopsy samples from larger muscle groups is warranted to confirm the amount of supplemented BA converted into carnosine.

The aim of this study was to perform a retrospective analysis from previous data to investigate the range of increases in the muscle carnosine content of the *m. vastus lateralis* following 4 weeks of BA supplementation, and determine the estimated amount of BA used for muscle carnosine synthesis. We hypothesised that there would be a low estimated incorporation of BA for muscle carnosine synthesis, though higher than previous studies, despite all individuals showing increased muscle carnosine content.

Method

Participants

Twenty-five active males (age 27 ± 5 years, height 1.74 ± 0.09 m, body mass 77.4 ± 11.5 kg) volunteered for the study and provided written informed consent. Participants were physically active (involved in non-structured exercise 1-3 times per week; e.g. cycling, running and team sports) and were requested to maintain similar levels of physical activity and dietary intake for the duration of the study; compliance with this request was verbally confirmed with individuals throughout. Individuals also completed a food diary during the supplementation period on two non-consecutive weekdays and one weekend day. Food diaries were analysed by a nutritionist for energy and macronutrient intake using specific software (Avanutri, Rio de Janeiro, Brazil). Additionally, the habitual dietary consumption of β-alanine was calculated using tables taken from the literature[11,12]. Participants were required not to have supplemented with creatine or BA in the 6 months prior to the study, not to be ingesting any dietary supplement except carbohydrate and whey protein, and to have an omnivorous diet, thus ingesting small quantities of BA in the diet. The study was first approved by the institution's Ethical Advisory Committee.

Experimental Design

This is a 4-week retrospective analysis using data from a randomized controlled trial published elsewhere[6]. Even though our study had a 24-week follow-up period, we opted for conducting the current analysis using the first 4 weeks because major increases in carnosine content occurred within this period. Participants attended the laboratory on two occasions, separated by four weeks of supplementation. Height and body mass (BM) were recorded upon arrival at the first laboratory session. Before and after the supplementation period, a biopsy sample was taken from the *m. vastus lateralis* and subsequently analysed for muscle carnosine content using HPLC.

Supplementation

Participants were randomly allocated to receive either BA (CarnoSyn®, NAI, USA) or placebo (PL; maltodextrin, NAI, USA) in a 2:1 ratio (i.e., two participants were allocated in BA for each participant in PL), and were supplemented with 6.4 g·day^{-1} of BA in sustained release tablets (N=17) or placebo (PL; N=8) for 4 weeks. To avoid any side-effects associated with BA supplementation, the dosing protocol was split over four times of the day at 3–4 hour intervals. Participants completed a log to verify adherence to the supplementation protocol. All individuals were included in the study regardless of level of adherence to the supplementation protocol since the subsequent analyses of BA use for muscle carnosine synthesis were individualised to the

total dose ingested based upon the self-reported adherence. Blinding occurred via an outside researcher not involved in direct data collection who provided the researchers with identical white pots containing only participant names.

Muscle biopsies

Muscle biopsies were taken using a 5 mm biopsy Allandale needle (Northern Hospital Supplies, Edinburgh, UK) by a method adapted from Bergstrom[13]. The dominant leg was prepared through an incision along the *m. vastus lateralis* muscle under local anaesthesia (lidocaine 1%, Linisol) of the skin. Muscle samples were taken and immediately frozen in liquid nitrogen and stored at -80 ºC. All biopsies followed the same standardised pattern across individuals. The location of each initial biopsy was at a point 25 cm proximal from the *tuberositas tibiae* and 5 cm lateral from the midline of the femoral course. The second incision was performed adjacent (~1 cm) to the first.

Chromatographic determination of carnosine

Total muscle carnosine content was determined by HPLC (Hitachi, Hitachi Ltd., Tokyo, Japan), according to the method of Mora, Sentandreu and Toldra[14]. All chromatography was carried out at room temperature. Samples were analysed in duplicate and injected via an auto sampler using a cut injection method with a total aspirated volume of 70 µL; 30 µL was discarded, 10 µL injected for analysis and the remaining 30 µL also discarded. Prior to all injections, samples were visually inspected for air bubbles, any of which were subsequently removed manually by the experimenter. Standard curves for carnosine were performed prior to each analysis session using concentrations of 0.1, 0.5, 1, 2.5, and 5 mM, showing excellent linearity (r^2 = 0.996 ± 0.005).

The method employed two mobile phases: Mobile phase A: 0.65 mM ammonium acetate, in water/acetonitrile (25:75). Mobile phase B: 4.55 mM ammonium acetate, in water/acetonitrile (70:30). Both solutions were adjusted to pH 5.5 using hydrochloric acid and thereafter filtered under vacuum through a 0.2 µm nylon filter membrane. The column used for chromatographic separation was an Atlantis HILIC silica column (4.6×150 mm, 3 µm; (Waters, Massachusetts, USA) attached to an Atlantis Silica column guard (4.6×20 mm, 3 µm). Separation comprised a linear gradient from 0 to 100% of solvent B in 13 min at a flow rate of 1.4 $mL \cdot min^{-1}$. Separation was monitored using an ultraviolet detector at a wavelength of 214 nm. Quantification was performed using peak areas, which were calculated by computer software coupled to the chromatographer and individually inspected for error and consistency by a researcher. Peak area for the standard curve was plotted and a regression equation obtained, from which interpolations were used to calculate the content. Limits of detection for the current method in our laboratory are 0.5125 $mmol \cdot kg^{-1}dm$. We have previously shown this method to be highly reliable in our laboratory, with inter- and intra-assay coefficient of variations (CV) of 0.9±1.2% and 4.0±4.5% (N=175).

Statistical Analyses

Data were analysed using the SAS statistical package (SAS 9.2, SAS Institute Inc., USA), and are presented as mean±1SD unless otherwise stated. The 95% confidence interval (95% CI) was calculated for muscle carnosine content and absolute changes therein. Muscle carnosine was analysed using a mixed model with individuals assumed as a random factor and supplementation (2 levels; BA and PL) and time (2 levels; Week 0 and 4) assumed as fixed factors. Tukey-Kramer adjustment for multiple comparisons were performed whenever a significant F-value was obtained and the significance level was set at $P \leq 0.05$. Food intake was compared between groups using a one-way mixed model with individuals assumed as a random factor and supplementation (2 levels; BA and PL) as a fixed factor. The amount of BA used for muscle carnosine synthesis was calculated by dividing the molar increase in muscle carnosine by the total ingested molar amount of BA and assuming that 40% of body mass is muscle mass[10]. The total ingested molar amount of BA was calculated based upon each individual's adherence to the supplementation protocol. Pearson's correlations were performed to determine any associations between initial muscle carnosine content, absolute changes, body mass and dietary intake.

Results

Muscle carnosine content was not different between groups at baseline (BA: 23.71 ± 6.85 mmol·kg^{-1}dm and PL: 21.72 ± 4.21 mmol·kg^{-1}dm, P=0.90), ranging from 11.67 to 44.78 mmol·kg^{-1}dm (95% CI: 20.46, 26.97 mmol·kg^{-1}dm) in BA and 15.14 to 27.14 mmol·kg^{-1}dm (95% CI: 18.80, 24.64 mmol·kg^{-1}dm) in PL. Supplementation increased muscle carnosine content by +11.0 ± 6.7 mmol·kg^{-1}dm (+51.7 ± 35.7%; P < 0.0001; FIGURE 1), with changes ranging from +2.42 to +22.10 mmol·kg^{-1}dm (95% CI: +7.85, +14.8 mmol·kg-1dm, +9.0 to +111.4%) in BA, and no change in PL (-0.63 ± 5.16 mmol·kg-1dm, 95% CI: -4.20, +2.94, P = 0.99).

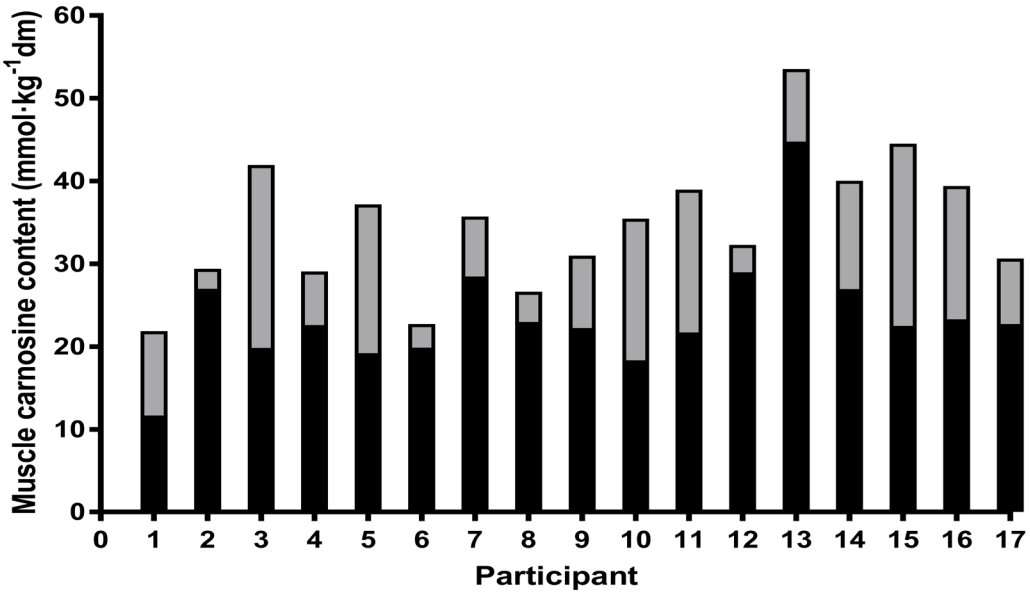

FIGURE 1 -Muscle carnosine content in all individuals supplemented with BA. Black bars represent initial muscle carnosine content (i.e., pre-supplementation) while the grey bars represent the increase in muscle carnosine (i.e., post-supplementation).

Adherence to the supplementation protocol was 93.8 ± 12.5% for the BA group (95.0 ± 5.5% for PL), equating to a total of 168.0 ± 22.4 g of BA ingested. The estimated amount of BA used for muscle carnosine synthesis was 39.4 ± 25.2 mmol, equivalent to 2.1 ± 1.2% (3.5 ± 2.2 g) of the total dose ingested (TABLE 1). Individual incorporation of BA ranged from 0.5 to 4.5% (0.8 to 8.1 g; TABLE 1).

Baseline carnosine content for BA was significantly correlated to post-supplementation content (r = 0.65, r^2 = 0.38, P = 0.009), but not the absolute change in carnosine (r = -0.28, r^2 = 0.08, P = 0.28) or the amount of BA used (r = -0.31, r^2 = 0.10, P = 0.22). The increase in muscle carnosine was significantly correlated to the amount of BA used (r = 0.95, r^2 = 0.90, P < 0.0001), but not to the total amount of BA ingested (r = 0.35, r^2 = 0.12, P = 0.16), while the estimated amount of BA used was not associated with the calculated amount of BA ingested (r = 0.35, r^2 = 0.12, P = 0.17). There was no significant correlation between body mass and increase in muscle carnosine (r = 0.03, r^2 = 0.001, P = 0.92).

There were no differences in food consumption during supplementation for energy intake or protein, carbohydrate and fat ingestion (all P > 0.05), while there was no difference in daily BA consumption from food sources between groups (P = 0.45; TABLE 2). BA intake from food sources was not correlated to the change in muscle carnosine content in the BA group (r = 0.03, r^2 = 0.001, P = 0.95).

TABLE 1 - Individuals changes in muscle carnosine content and estimated amount of β-alanine (BA) used for carnosine synthesis

Participant number	Increase in Carnosine (mmol·kg^{-1})	Compliance to Supplementation (%)	Total BA Ingested (g)	Estimated BA incorporated (g)
1	10.21	83.0	148.8	3.48
2	2.42	100.0	179.2	0.83
3	22.10	94.6	169.6	6.89
4	6.47	100.0	179.2	1.91
5	18.01	100.0	179.2	8.11
8	2.89	99.1	177.6	0.87
10	7.23	88.4	158.4	2.09
13	3.63	92.9	166.4	1.40
14	8.73	87.5	156.8	2.39
16	17.11	100.0	179.2	5.16
17	17.24	100.0	179.2	5.07
18	3.31	50.0	89.6	0.95
19	8.76	100.0	179.2	2.80
22	13.08	98.7	176.8	3.65
23	22.03	100.0	179.2	5.99
25	16.11	100.0	179.2	5.60
26	7.90	100.0	179.2	2.53
Mean	11.01	93.8	168.0	3.51
1SD	6.66	12.5	22.4	2.25

TABLE 2 - Food intake (mean ± 1SD) in BA and PL during supplementation.

	BA	PL
Energy (kcal·day^{-1})	2297 ± 436	2195 ± 628
Carbohydrate (g·day^{-1})	258 ± 50	259 ± 99
Protein (g·day^{-1})	115 ± 28	107 ± 45
Fat (g·day^{-1})	90 ± 25	81 ± 28
β-alanine (g·day^{-1})	0.8 ± 0.5	0.7 ± 0.4

Discussion

Following 4 weeks of BA supplementation at 6.4 g·day^{-1}, the estimated amount of ingested BA used to increase *m. vastus lateralis* carnosine content was extremely low, confirming previous results using ^{1}H-MRS and other muscle groups[9,10]. These data demonstrate that very little of the BA ingested during supplementation is used for muscle carnosine synthesis and suggests that further work to optimise BA supplementation in humans could lead to greater increases in muscle carnosine content.

Previous determination of the amount of BA converted to carnosine has suggested this to be low (for review see Blancquaert, Everaert and Derave[9]), although these studies based their calculations on changes in muscle carnosine as measured by ^{1}H-MRS in smaller muscle groups. Furthermore, it is unclear whether these calculations were based upon the calculated amount of BA ingested (i.e., daily dose x time) or per the actual amount of BA ingested, as determined by adherence to the supplementation protocol. Nonetheless, the estimated amount of BA used for muscle carnosine synthesis in the current study was approximately 2%, confirming previous work, and ranged from as little as 0.5 to 4.5%.

Therefore, although all individuals could increase muscle carnosine content, the clear majority of BA was not used for muscle carnosine synthesis, although this assumption is based upon a carnosine turnover of zero, which is improbable. The increases in muscle carnosine content shown here were not related to body mass, suggesting that the amount of BA used for muscle carnosine synthesis does not depend on the muscle mass of the individual, although further studies should determine this based upon actual lean mass and not an estimate. Further research should elucidate whether different doses lead to greater gains in muscle carnosine content and higher estimated use of BA for synthesis.

Muscle carnosine was increased by +11.01 mmol·kg^{-1}dm, which is slightly higher than increases shown by Harris et al.[1] and Hill et al.[5], who also employed lower doses (mean: 5.2 g·day^{-1}). All individuals increased muscle carnosine content with supplementation, although the range of increases was large, from +2.42 to +22.10 mmol·kg^{-1}dm. The change in muscle carnosine was not correlated to initial content, which suggests that individuals with higher or lower initial content are not predisposed to lower or higher gains with BA supplementation. Indeed, four weeks of BA supplementation is not sufficient to saturate muscle carnosine content[5,6], meaning that all individuals employing a short-term supplementation strategy identical to the one used here will likely increase muscle carnosine content to some extent, although not to their maximum storage capacities. However, future studies should elucidate why some individuals respond more than others, and the physiological mechanisms determining these responses.

It must be acknowledged that the calculations used are based upon the assumption that carnosine turnover over 4 weeks is zero, which is unlikely to be the case but also impossible to determine at this point. Nonetheless, we can still speculate as to the fate of the remaining BA not converted to carnosine and how to optimise synthesis with supplementation. It is possible that most of the BA was oxidised by hepatic and renal transaminating enzymes which have been shown to tightly control circulating levels of BA[15]. It has been suggested that higher single doses of BA (i.e., >1.6 g) may saturate these enzymes, thus leading to greater gains in carnosine accretion[16]. However, muscle carnosine loading with prolonged BA supplementation is most pronounced during the first four weeks of supplementation[5,6]; this is also true of the first vs. subsequent twelve days of supplementation[17]. That supplementation is more effective at increasing muscle carnosine in the initial phase appears incompatible with the theory of enzyme saturation. It has recently been suggested that a decline in histidine availability may be a limiting factor in carnosine accretion with BA supplementation, although co-supplementation with histidine did not lead to further increases in muscle carnosine[17], while a reduction in the transport of BA into muscle via the transporter *TauT* is another possibility[6]. Potential strategies to improve BA transport into muscle may include co-ingestion with meals, since *TauT* activity may be enhanced by insulin secretion[10], or following exercise which may lead to a contraction-induced stimulation of *TauT*[18]. A downregulation of carnosine synthesis or upregulation of degradation can also not be excluded as a limiting factor to carnosine accumulation with BA supplementation. Further research should ascertain the mechanisms by which increases in muscle carnosine may be optimised with supplementation.

In conclusion, the estimated amount of BA used for carnosine synthesis based upon increases in carnosine content of the *m. vastus lateralis* after 4 weeks of supplementation was low, confirming previous results using ^{1}H-MRS and smaller muscle groups. These data suggest that current recommended dosing regimens may be sub-optimal and more studies are required to better understand BA metabolism and optimize carnosine loading in human skeletal muscle.

Resumo

Baixa eficiência da suplementação de beta-alanina para o acúmulo de carnosina muscular: uma análise retrospectiva de um estudo de 4 semanas

A suplementação de β-alanina (BA) é capaz de aumentar o conteúdo de carnosina muscular, entretanto, a eficiência em relação à quantidade de BA usada para carnosina é baixa. No entanto, questões metodológicas

podem ter subestimado a quantidade de BA utilizada. O objetivo desse estudo foi determinar a estimativa da quantidade de BA convertida em carnosina muscular usando uma análise retrospectiva de um estudo controlado randomizado de quatro semanas que investigou os efeitos da suplementação de BA no conteúdo de carnosina muscular no m. vasto lateral. Vinte e cinco homens (idade 27 ± 5 anos, altura 1,74 ± 0,09 m, massa corporal 77,4 ± 11,5 kg) foram suplementados com 6,4 g · dia 1 de BA (N = 17) ou placebo (PL; N = 8) por 28 dias. Foi realizada uma biópsia muscular nos participantes pré e pós-suplementação e posteriormente analisada o conteúdo de carnosina muscular usando HPLC. Os dados foram analisados utilizando modelos mistos e correlações de Pearson. O conteúdo de carnosina muscular aumentou em + 11,0 ± 6,7 mmol · kg^{-1}dm (P <0,0001) em BA, sem alteração em PL (P = 0,99). A quantidade estimada de BA convertida em carnosina muscular foi de 2,1 ± 1,2% (intervalo: 0,5 a 4,5%) da dose total ingerida. As correlações de Pearson mostraram que a carnosina pré-suplementação foi correlacionada com a carnosina pós-suplementação no grupo BA (r = 0,65, r^2 = 0,38, P = 0,009), mas não a mudança absoluta na carnosina (r = -0,28, r^2 = 0,08, P = 0,28) ou a quantidade de BA utilizada (r = -0,31, r^2 = 0,10, P = 0,22). A quantidade estimada de BA ingerida utilizada para síntese de carnosina foi extremamente baixa após 4 semanas de suplementação de BA em 6,4 g · dia^{-1}. Os dados sugerem que muito pouco do BA ingerido é usado para síntese de carnosina muscular e destaca o potencial de trabalho adicional para aperfeiçoar a suplementação de BA em humanos.

Palavras-chave: Síntese de Carnosina; Incorporação de Beta-Alanina; Otimização; Estratégias de Suplementação; Cromatografia Líquida de Alta Performance.

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