NUTRITION RESEARCH XX (2012) XXX–XXX

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L-glutamine absorption is enhanced after ingestion of L-alanylglutamine compared with the free amino acid or wheat protein

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ARTICLE INFO

Article history:
Received 2 September 2011
Revised 14 February 2012
Accepted 16 February 2012

Keywords:
L-glutamine
L-alanylglutamine
Wheat protein
Absorption
Supplements
Males

ABSTRACT

Differences in plasma L-glutamine (L-Gln) concentrations from ingestion of different formulations of L-Gln were examined in 8 men (26.8 ± 4.2 years old, 181.1 ± 10.9 cm, 85.8 ± 15.4 kg). Subjects reported to the laboratory on 4 separate occasions and randomly consumed 1 of 4drinks containing 60 mg/kg of L-Gln; 89 mg/kg of Sustamine (L-alanylglutamine [AlaGln]; Kyowa Hakko Europe GmbH, Düsseldorf, Germany), which contained an equivalent L-Gln dose as consumed in L-Gln); 200 mg/kg of an enzymatically hydrolyzed wheat protein (HWP) with an L-Gln content of 31 mg/kg; or a control that consisted only of water. It was hypothesized that the AlaGln trial would increase plasma glutamine concentrations greater than the other experimental trials. Ingestion of L-Gln, AlaGln, and HWP resulted in significant increases in the plasma L-Gln concentration, peaking at 0.5, 0.5, and 0.75 hours, respectively. The corresponding mean peak increases were 179 ± 61, 284 ± 84, and 134 ± 36 μmol/L, respectively. Concentrations returned to baseline in all subjects by 2 hours after L-Gln and HWP and by 4 hours after AlaGln. Mean areas under the plasma concentration curve, calculated between 0 and 4 hours, were 127 ± 61, 284 ± 154, and 151 ± 63 $\mu mol \cdot h \cdot L^{-1}$ for L-Gln, AlaGln, and HWP, respectively. When allowance was made for the lower L-Gln dose administered as HWP, the peak plasma concentration and area under the plasma concentration curve were approximately the same as for AlaGln. The results suggest a greater transfer from the gut to plasma of L-Gln when supplied as AlaGln and possibly also as HWP compared with when the same dose was provided as the free amino acid.

1. Introduction

L-glutamine (L-Gln), synthesized from glutamate and ammonia, is a neutral amino acid that is readily transported across plasma membranes [1]. An important intermediate in several metabolic pathways, cellular use of L-Gln can far exceed that of other amino acids particularly within intestinal and immune cells [2,3]. Of the proteogenic amino acids in man, L-Gln provides 50% of the free amino acid pool, with normal concentrations in the range of 0.5 to 0.8 mmol/L in plasma and 20 to 25 mmol/L in muscle intracellular water [4,5]. L-glutamine exhibits several metabolic roles; for example, it is an important form of transport of amino nitrogen and ammonia and a substrate in gluconeogenesis and ammonia-

Abbreviations: AlaGln, L-alanylglutamine; AUC, area under the plasma concentration curve; HWP, hydrolyzed wheat protein; L-Gln, L-glutamine; CTL, control.

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doi:10.1016/j.nutres.2012.02.003

genesis [6,7]. L-glutamine is an important fuelsource for several types of rapidly dividing cells [8] and may be involved in the regulation of protein synthesis [9]. L-glutamine is also the preferential fuel source for intestinal enterocytes [10] where it is involved in the maintenance of intestinal structure and function [6,8,11,12].

Under normal conditions, L-Gln requirements are met by synthesis within specific tissues, principally skeletal muscle [1,13], and, to some extent, from dietary protein. About 50% to 60% of dietary L-Gln is taken up by intestinal cells. The high rate of L-Gln use by the intestine may be partially attributed to the large lymphocyte and macrophage populations in intestinal walls and Peyer patches. These cells exhibit high glutaminase activity and use L-Gln as their preferential fuel source even in the quiescent state [14-16]. However, aswith other cells that require L-Gln, both enterocytes and lymphocytes lack the synthetic apparatus to produce it and, therefore, rely solely on circulatory or dietary sources, a fall that can potentially compromise function [2,4,14].

Under most conditions, L-Gln is considered to be a nonessential amino acid. However, during stressful situations such as burn injuries, sepsis, surgery, and excessive training, L-Gln concentrations may fall below normal levels. After surgery, plasma L-Gln levels have been shown to decline, and when L-Gln-free solutions are infused, pancreatic exocrine and gut mucosal cells can become atrophied, and the integrity of the gut is compromised [6,8,17]. This impairment appears to be diminished, though, when L-Gln is reintroduced in these solutions [6,18,19]. L-glutamine ingestion has also been reported to increase electrolyte and water absorption during dehydration resulting from intestinal infections [20-23] and exercise [24]. The use of oral L-Gln supplementation has also been shown to reduce the incidence of illness after prolonged exercise [25].

When L-Gln is ingested as a supplement, it is often supplied in liquid form, usually of low pH to enhance palatability and to reduce microbial growth. Under such conditions, L-Gln is unstable and may be unable to providephysiologic benefit [26,27]. Recent evidence suggeststhat when glutamine is bound as a dipeptide, such as L-alanylglutamine (AlaGln), its stability, especially at a low pH, appears to be enhanced [20,28,29]. However, studies comparing the absorption differences of L-Gln in its free form, as a dipeptide or as a polypeptide, are limited. The purpose of this study was to compare plasma concentration of glutamine after administration of L-Gln supplied in the free form to a near-equivalent dose of L-Gln supplied either as a dipeptide with alanine or as a polypeptide produced from the hydrolysis of wheat protein. It was hypothesized that ingestion of the alanylglutamine dipeptide would increase plasma glutamine concentrations greater than the other methods of glutamine ingestion.

2. Methods and materials

2.1. Subjects

Eight male volunteers (26.8 ± 4.2 years old, 181.1 ± 10.9cm, 85.8 ± 15.4 kg) with no known or recognized symptoms of infection or disease or metabolic or physiologic disorder volunteered for this study. The study and its aims were explained to each subject before their consent was obtained. Ethical approval for the study was obtained according to the Institute of Naval Medicine regulations set down in the Schedule of Approved Procedures and by the Ministry of Defence (UK) Personnel Research Ethical Committee and from the ethics committee of the University College Chichester.

2.2. Experimental protocol

Subjects reported to the laboratory on 4 separate occasions and randomly consumed 1 of 4 drinks: 60 mg/kg of L-Gln; 89 mg/kg of Sustamine (AlaGln; Kyowa Hakko Europe GmbH, Düsseldorf, Germany), which contained an equivalent L-Gln dose as consumed in L-Gln; 200 mg/kg of an enzymatically hydrolyzed wheat protein (HWP) (type WGE80GPA; DMV International Nutritionals, New York, NY) with a L-Gln content of 31 mg/kg; or a control (CTL) that contained only 250 mL of water. All configurations of L-Gln were dissolved in 250 mL of water to which 20 mL of lemonade was added to improve the taste. A minimum of 3full days separated each experimental session, whereas the entire study was completed within 3 weeks. The order of treatments was randomized using a Latin square design.

The L-Gln dose of 60 mg/kg body mass was based on published work [30], whereas the ingestion of 200 mg/kg HWP was arrived at for reasons of palatability (mean dose ofHWP ingested, 17 g). The L-Gln content of the HWP wasassayed according to Kuhn et al [31] and shown to be 19.94 g per 100 g of protein. An L-Gln content of 15.5 g per100 g HWP was, therefore, calculated, assuming this tocontain 77.6% by weight of protein (type WGE80GPA). The dose of200 mg/kg HWP was, therefore, equivalent to 31mg/kg L-Gln.

On each trial day, the subjects arrived at the laboratory in the morning after an overnight fast of 10 hours. No food or drink, apart from water, was consumed before the test. A 2-mL blood sample was taken 10 minutes before ingestion of the treatment via a catheter inserted into an antecubital vein. Starting at 9 AM for the first subject, the treatment dissolved in 250 mL was ingested and followed with a further 50 mL ofwater. Subjects were processed in pairs, with 5 minutes between each pair. Two milliliters of blood samples were collected after 15, 30, 45, 60, 75, and 90 minutes and 2, 2.5, 3, 4, 5, and 6 hours. Subjects were allowed to consume water after 2 hours, but no food was given until completion of the 6hours. All subjects were processed on each trial day, and relative and absolute timings were kept constant over the course of the study.

2.3. Blood analysis

Blood samples were dispensed into tubes containing lithium heparin as an anticoagulant, stored temporarily on ice, then harvested for plasma within 15 minutes. Plasma wasstored at −70°C until analyzed during the following 2weeks. L-glutamine was assayed enzymatically with asparaginase and glutamate dehydrogenase according to Routledge et al [32] adapted for use on a Cobas Miras autoanalyzer (West Sussex, UK). The procedure involves rapid thawing of samples and extraction of an aliquot with ice-cold perchloric acid followed by neutralization of the acid extract with potassium bicarbonate.

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2.4. Statistical analyses

Areas under the plasma concentration curve (AUCs) over the first 4 hours or until the observed plasma concentration fell below the baseline concentration (AUC) were calculated according to the trapezoidal rule. Comparisons of AUC between experimental sessions were accomplished with a one-way analysis of variance. In the event of a significant Fratio, Tukey post hoc tests were used for pairwise comparisons. Data are presented as mean ± SD.

3. Results

Baseline plasma L-Gln concentrations before each of the treatments (L-Gln, AlaGln, HWP, and CTL) were 463 ± 8 6, 475 ± 108, 471 ± 74, and 510 ± 72 μmol/L, respectively. No significant differences were noted. There was no significantchange in the plasma L-Gln concentration with the CTL treatment over the 6 hours (see Fig. 1A). The weighted within-subject square root of variance in the plasma L-Gln concentration, that is, s_{ind}, was 8.9 μmol/L.

The mean change in plasma concentrations after the 4treatments is shown in Fig. 1. All subjects showed an increase in plasma L-Gln after ingestion of L-Gln, with a mean peak increase of 179 ± 61 μmol/L (Table 1) occurring with a median time of 0.5 hours. Plasma concentrations of L-Gln returned to within ±50 μmol/L of the initial concentration by 2 hours. The mean area under the concentration curve between 0 and 4 hours was 127 ± 61 $\mu mol \cdot h \cdot L^{-1}$.

All subjects showed an increase in plasma L-Gln after ingestion of AlaGln (Table 1). The peak increase after AlaGln was greater than 10% in 6 of 8 subjects compared with that after L-Gln. The mean peak increase was 284 ± 84μmol/L or 159% of that after L-Gln. The greater increase after AlaGln was statistically greater than L-Gln ($P < .05$). The plasma concentration remained elevated longer after AlaGln returning to ±50 μmol/L of the initial mean concentration in all subjects by 4 hours. Mean AUC for the period 0 to 4 hours was 284 ± 154 $\mu mol \cdot h \cdot L^{-1}$, 224% of that after L-Gln ($P < .05$).

Of 8 subjects, 7 showed an increase in plasma L-Gln after ingestion of HWP (Table 2). In the case of the eighth subject (subject D), no discernible peak in the plasma concentration was apparent. Excluding the data from subject D, the median time to peak after ingestion of HWP was slightly longer (0.75 hours) than with L-Gln. At the dose given, the mean peak increase was 134 ± 36 μmol/L or 84% of that with L-Gln (data from subject D were excluded). The difference between treatments (with subject D excluded) was not significantly different ($P > .05$). The mean peak increase was significantly lower ($P < .05$) than that observed with AlaGln (278 $\mu mol \cdot h \cdot L^{-1}$ with subject D excluded). When adjustment was made for the lower L-Gln content of HWP (31 compared with 60 mg/kg for both L-Gln and AlaGln), the predicted mean increase of 259 ± 70 μmol/L was significantly greater ($P < .05$) than the increase after L-Gln (160 ± 33 μmol/L; subject D was excluded) but now within 7% of that after AlaGln. Excluding the data from subject D, the concentration declined after the peak to a concentration of ±50 μmol/L of the initial concentration at 2 hours. Mean AUC for the period 0 to 4 hours was 151 ± 63 $\mu mol \cdot h \cdot L^{-1}$. The mean in this case was 119% of that after L-Gln (data from subject D were excluded). The difference in AUC between treatments was not significant ($P > .05$). If the estimates ofAUC for HWP are adjusted upwards to allow for the lowerdose of L-Gln, the predicted mean AUC is 293 ± 121 $\mu mol \cdot h \cdot L^{-1}$, 231% of that after L-Gln ($P < .05$). Compared with AlaGln, AUC with HWP was 51.4% before and 99.5% after adjustment for the lower dose of L-Gln. The difference in AUC for the 2 treatments, even before adjustment for the lower L-Gln dose, was not significantly different ($P > .05$).

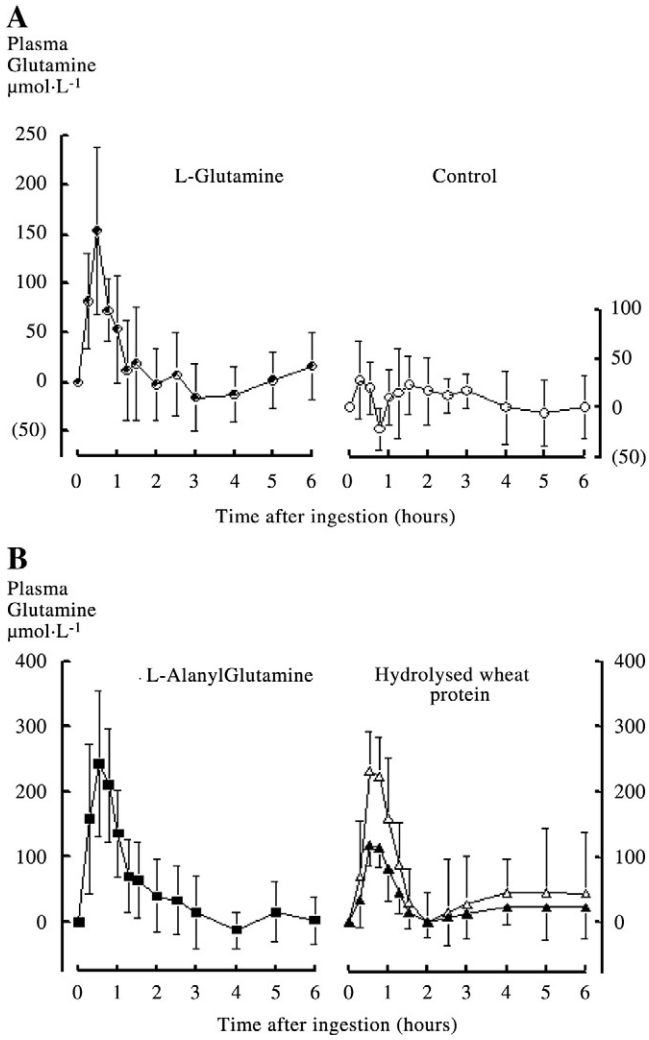

Fig. 1 – A, The mean change in the plasma L-Gln concentration after ingestion of 60 mg/kg L-Gln or plain water (CTL). B, The mean change in the plasma L-Gln concentration after ingestion of 89 mg/kg AlaGln and 200mg/kg HWP (filled triangles). Also shown are the predicted mean plasma L-Gln concentrations (open triangles) after ingestion of 387 mg/kg HWP containing an equivalent amount of L-Gln to that administered as L-Gln (A) or AlaGln (B). The prediction is made based on a linear response in plasma concentration with increasing dose. For reasons of clarity, mean values minus SD are shown for the measured changes with 200 mg/kg HWP and plus SD for the predicted changes with 387 mg/kg HWP.

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Table 1 – Peak plasma L-Gln concentration in response to the ingestion of 60 mg/kg L-Gln and 89 mg/kg AlaGln, the change (Δ) from the immediate pretreatment concentration to the peak, and the AUC calculated over 0 to 4 hours

Subject	Treatment, L-Gln				Treatment, AlaGln			
	Time to peak, h	Peak concentration, μmol/L	Δ at peak, μmol/L	AUC, μmol·h·L^{-1}	Time to peak, h	Peak concentration, μmol/L	Δ at peak, μmol/L	AUC, μmol·h·L^{-1}
A	0.50	696	118	75	0.75	885	231	205
B	0.50	672	199	111	0.50	827	375	516
C	1.00	687	167	236	0.50	896	413	544
D	0.50	669	308	128	0.25	923	322	208
E	0.25	622	175	88	0.25	511	161	178
F	0.50	620	122	64	0.25	601	219	195
G	0.50	701	196	112	0.50	751	252	175
H	0.50	464	146	202	0.75	677	295	249
Mean SD	0.50[a]	641	179	127	0.50[a]	759	284	284
		78	61	61		151	84	154
Less subject D								
Mean less D		637	160	127		735	278	294
		83	33	66		147	89	163

[a] Median time given.

4. Discussion

Results of this study indicated that increases in plasma L-Gln concentrations were greater after AlaGln ingestion than with either of the other 2 experimental treatments. The changes in the plasma L-Gln concentration, peaking at 0.5 hours after ingestion of L-Gln and returning to baseline after 1 to 2 hours, were similar to those reported earlier by Ziegler et al [33] and Castell and Newsholme [30]. Changes in plasma L-Gln after administration with AlaGln are comparable with the data of Klassen et al [34] and Hoffman et al [24]. The results of this study further demonstrate the potential of HWP to act as a source of dietary L-Gln, although earlier studies in humans [35] and horses [32] have shown increases in plasma after the ingestion of a protein-containing meal. Castell et al [35] demonstrated a peak in plasma L-Gln concentration 2 hours post food independent of meal timing, with protein meals producing the greatest response.

The HWP from DMV International Nutritionals is known to contain a mixture of short- and long-chain peptides with a measured overall glutamine content of 15.5% by weight. The rapid increase in plasma L-Gln with the peptide mixture, peaking only slightly later than the free amino acid, is consistent with it being a viable dietary source of L-Gln. Based on the results of 7 subjects, the mean response (measured as AUC) was approximately the same as that when 60 mg/kg of L-Gln was ingested despite the much lower amount of L-Gln in the dose of HWP ingested. It is

Table 2 – Peak plasma L-Gln concentration in response to the ingestion of 200 mg/kg HWP, the change (Δ) from the immediate pretreatment concentration to the peak, and the AUC calculated over 0 to 4 hours

Subject	Treatment, HWP				Predicted values for a dose of 387 mg/kg body weight	
	Time to peak, h	Peak concentration, μmol/L	Δ at peak, μmol/L	AUC, μmol·h·L^{-1}	Δ at peak, μmol/L	AUC, μmol·h·L^{-1}
A	0.75	708	160	112	310	217
B	0.75	610	95	64	184	125
C	1.00	671	174	243	336	471
D	NDP	NDP	NDP	–	–	–
E	0.50	579	176	192	341	372
F	0.50	637	118	194	228	376
G	0.75	627	125	103	242	199
H	0.50	414	89	150	173	291
Mean	0.75[a]	607[b]	134[b]	151[b]	259[b]	293[b]
SD		95	36	63	70	121

Also shown are the predicted values after ingestion of 387 mg/kg (equivalent to an L-Gln dose of 60 mg/kg). NDP indicates no discernible peak.
[a] Median time given.
[b] Mean value (SD) of all subjects less subject D.

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suggested that had equivalent amounts of the L-Gln been administered, AUC after HWP would have been double to that with L-Gln and close to that of AlaGln. This, however, assumes an approximate doubling in AUC with an equivalent increase in the dose of HWP administered, which may not hold true. However, if this is the case, then the plasma changes would suggest an equal transfer availability of L-Gln from AlaGln and HWP, in either case, twice that seen with L-Gln itself. A possible explanation of this may be the presence of specific dipeptide transporters within the mucosal cells of the human small intestine [36,37]. Evidence for the presence of such a transport system was suggested by studies in man [38] where a given quantity of glycine was absorbed faster when administered orally as a dipeptide or tripeptide compared with the free form. This was confirmed in subsequent studies in humans using quantitative perfusion techniques of individual dipeptides [39] and in rats with the use of protein hydrolysates [40]. Because uptake of L-Gln is dependent on a monoamine transport system [41], transport of the free amino acid after administration of high doses may be limited by the availability of carrier sites. Thus, the availability of carrier systems for oligopeptides as well as free amino acids may allow a more rapid transit from the intestinal lumen into the mucosal cells. An alternative interpretation of the results is that the apparently lower transfer into plasma of L-Gln with L-Gln reflects a higher rate of extraction by the small intestine. As a result, AlaGln (and possibly HWP) may be less effective in supporting gut cell function, although more effective in meeting cellular functions that rely upon plasma-borne L-Gln. From a commercial standpoint, the provision of stable liquid supplements containing free L-Gln is not possible, so at a practical level, drinks containing AlaGln may still be superior to a drink containing L-Gln in supporting gut function despite a lower rate of extraction.

Comparison between AlaGln and HWP did not result inany significant difference in the transfer of L-Gln, when the amount of L-Gln in HWP was equivalent to that provided in AlaGln. However, the time course of the peak increase was different. Peak elevations in plasma glutamine concentrations occurred at a median time of 0.5 hours withAlaGln while occurring at a median time of 0.75 hours with HWP. A recent study has suggested that AlaGln ingestion can increase time to exhaustion during a mild hydration stress [24]. The benefits of enhancing electrolyte and fluid absorption have been seen by others well [20], suggesting that a method of ingestion that provides a more efficient rate of absorption would be more suitable for athletic populations.

The main limitations to the study are firstly that only 1dose level of each treatment was used, and although L-Gln and AlaGln were matched to each other, this was not so in the case of HWP. A dose of 60 mg/kg of L-Gln (~5 g in an 80-kg subject) was selected based on previously published work [30]. The dose of 89 mg/kg of Sustamine was chosen to match the former on a molar basis. Because of palatibility issues and the need to keep ingested fluid volumes equal, 200 mg/kg of HWP was given, which had just half the L-Gln content of either the L-Gln or AlaGln treatments.

Although we tried to overcome this second limitation bycalculation, confirmation of the relative effectiveness of HWP in transferring L-Gln into plasma would require comparison of, for example, 200 mg/kg of HWP with 30 mg/kg of L-Gln and 44.5 mg/kg of Sustamine. A further limitation of the study is the absence of any data on the fate of L-Gln absorbed through, for instance, the measurement of citrulline and glycine in plasma [42,43], both of which are released with glutamine extraction in the small intestine.

In conclusion, the results of this study indicate that L-Gln ingested as a dipeptide (AlaGln) or possibly oligopeptide (HWP) in fluid increased the amount of L-Gln tranferred to plasma relative to that provided by the free-form amino acid. In consideration of the time course of peak concentration of L-Gln in plasma, the hypothesis that AlaGln ingestion can increase plasma glutamine concentrations greater that the other methods of ingestion is accepted.

Acknowledgment

The authors are grateful to DMV International Nutritionals, Fraser, New York, NY, for financial support of this study and the supply of HWP. The authors also acknowledge Kyowa Hakko Europe for their supply of Sustamine.

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Please cite this article as: Harris RC, et al, L-glutamine absorption is enhanced after ingestion of L-alanylglutamine compared with the free amino acid or wheat protein, Nutr Res (2012), doi:10.1016/j.nutres.2012.02.003