The effects of large neutral amino acid supplements in PKU: An MRS and neuropsychological study

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Abstract

Objective: To determine the effects of large neutral amino acid (LNAA) supplements on brain and plasma phenylalanine (Phe) levels and other metabolites in early treated subjects with classical phenylketonuria (PKU), and to investigate the relationship between these metabolites and neuropsychological performance.

Methods: This was a prospective, double blind, cross over study consisting of four two-week phases with a 4 week washout period. Sixteen subjects (7 males), with classical PKU were recruited into the study and completed all 4 phases. Each phase consisted of either the LNAA supplement or placebo, and either the patient’s usual medical product or not. Subjects were instructed to follow their usual Phe restricted diet, maintain energy intake and complete a 3-day food record during each phase. At the end of each phase, brain Phe and other metabolites were measured by proton magnetic resonance spectroscopy (MRS), and plasma amino acids quantified. A detailed neuropsychological assessment was performed on the same day as the MRS and plasma collection.

Results: There was no correlation between plasma and brain Phe, but few of the plasma Phe readings were over 1200 μmol/L. Plasma Phe decreased with LNAA supplementation when patients were not taking their medical formula. LNAA supplementation had a specific impact on executive functions particularly in verbal generativity and cognitive flexibility. Measures of attention were better on medical product, with or without LNAA supplements.

Conclusions: LNAA supplementation was associated with a trend to a lowering of plasma Phe levels. LNAA supplementation had a specific impact on executive functions particularly in verbal generativity and flexibility. For individuals already complying with diet and PKU medical product, additional supplementation with LNAA is of limited value. LNAA supplementation may be of benefit to those unable to comply with PKU medical product by reducing plasma Phe, perhaps by competing with Phe at the level of transport across the gut.

Keywords: Phenylketonuria; Brain–plasma barrier; Magnetic resonance spectroscopy; Large neutral amino acids; Amino acid transport

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Introduction

Phenylalanine is a known neurotoxin and untreated individuals with phenylketonuria (PKU) with high plasma phenylalanine (Phe) levels usually develop severe intellectual disability [1]. In contrast, general cognitive ability is within the normal range in individuals with PKU treated with a low Phe diet from the neonatal period [2]. However, studies have shown that even early-treated individuals with PKU may develop subtle cognitive abnormalities. Neuropsychological studies suggest a specific cognitive profile in which reduced attention, reaction time and executive functioning are most commonly observed [3,4]. While intellectual impairment is thought to be irreversible, it has been suggested that the specific deficits observed in early-treated PKU may be reversible. Indeed, there is evidence suggesting that neuropsychological test performance is more closely related to concurrent plasma Phe levels than to long-term dietary control, and that dietary interventions that induce relatively small changes in plasma Phe levels can improve neuropsychological performance as Phe levels decrease [5,6]. Behaviour, in particular levels of depression and anxiety, has also been found to differ between early treated PKU and unaffected peers [7].

A puzzling finding is that a small proportion of untreated individuals with PKU have preserved cognitive abilities despite having significantly elevated plasma Phe levels [8–10]. This has led to the speculation that there may be individual differences in the permeability of the central nervous system to Phe, which could have a protective effect on brain function. Findings from international studies using proton magnetic resonance spectroscopy (MRS) to measure in vivo levels of certain metabolites in the brain have supported this hypothesis; individuals may have similar plasma Phe levels yet their brain Phe levels may be very different. Intellectual outcome was more closely related to brain Phe levels than plasma Phe levels [11,12].

To date there appear to have been no published investigations of the relationship between brain Phe concentrations and performance on tests of the specific cognitive or behavioural functions that are typically found to be impaired in persons with phenylketonuria. It has been proposed that supplementation of the Phe restricted diet with large neutral amino acids (LNAA) might be a successful adjunct to treatment, may have a beneficial effect on mood and cognition [13–15], and may offer a neuroprotective effect by competing with Phe for transportation through the plasma–brain barrier [8,12,13].

In this study, we have attempted to evaluate the potential role that LNAA added to the amino acid products used for PKU might play in the regulation of Phe transport across the brain–plasma barrier, and have examined the relationship between LNAA supplementation and cognitive and affective outcome under four different therapeutic combinations.

Methods

Subjects

Sixteen subjects with early treated classical PKU (plasma levels at some stage >1000 μmol/L) were recruited into the study (7 males, 9 females, median age 24 y 9 m range 11 y 8 m–45 y 1 m), all currently on diet and medical products for PKU. All subjects had been treated at The Children’s Hospital, Westmead (CHW), and were recruited via letter invitation or telephone contact. Informed consent was obtained for all subjects, and the study was approved by The Children’s Hospital at Westmead Ethics Committee.

Clinical protocol

This study was a prospective, double blind, cross over study. Subjects completed four phases as outlined below. Subjects were required to stay on each phase for 14 days with a 4 week minimum washout period between phases.

The four phases of the study were as follows:

Phase 1: medical product/active phase. Subjects took their usual medical product, took placebo tablets and maintained their usual Phe restricted diet and medical product, took LNAA (active) tablets and maintained their usual Phe restricted diet and energy intake.

Phase 2: medical product/placebo phase. Subjects took their usual medical product, usual Phe restricted diet and placebo tablets. This phase is equivalent to usual treatment.

Phase 3: no medical product/active. Subjects did not take their usual medical product, but took LNAA (active) tablets and maintained their usual Phe restricted diet and energy intake.

Phase 4: no medical product/placebo. Subjects did not take their usual medical product, took placebo tablets and maintained their usual Phe restricted diet and energy intake.

LNAA dosage was 250 mg/kg/day, based on actual weight or ideal weight if the subject was overweight. The subjects took three equal daily doses consumed with breakfast, lunch and dinner. The composition of the 400 mg LNAA tablets is shown in Table 1. Left-over tablets were collected at the end of each phase and counted, in order to assess compliance.

Placebo tablets were compounded to match the appearance of the active tablets. Both the LNAA and placebo tablets contained menthol to mask the LNAA taste. Subjects and investigators were blinded as to the order of the phases, which were randomly allocated by a Hospital

Table 1

Composition of LNAA powder mix (amounts shown are gram per 100 g of LNAA powder)

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>g/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Histidine</td>
<td>15.11</td>
</tr>
<tr>
<td>L-Isoleucine</td>
<td>7.53</td>
</tr>
<tr>
<td>L-Leucine</td>
<td>7.53</td>
</tr>
<tr>
<td>L-Lysine</td>
<td>7.53</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>15.11</td>
</tr>
<tr>
<td>L-Threonine</td>
<td>7.53</td>
</tr>
<tr>
<td>L-Tryptophan</td>
<td>15.11</td>
</tr>
<tr>
<td>L-Tyrosine</td>
<td>15.11</td>
</tr>
<tr>
<td>L-Valine</td>
<td>7.53</td>
</tr>
</tbody>
</table>
Pharmacist, and codes were not broken until a subject had completed all four phases of the study.

All subjects were still on a phenylalanine restricted diet. Of the total 16 subjects, 14 had been treated from infancy. The other two subjects had been diagnosed by the wet urine test, one detected at age 3.5 months, and the other at age 2 years, 4 months. The CHW PKU clinic uses either a Phe exchange system or a protein counting method to monitor Phe intake but 13 subjects were not rigorously counting their Phe or protein intake each day. Blood Phe levels for the previous year were used to determine each subject’s pre study Phe control No. subject achieved excellent control (median Phe level <450 mol/L). Nine subjects were determined to have ‘good’ control (median Phe level 450–750 mol/L), 6 subjects had ‘marginal’ control (median Phe level 750–1000 mol/L) and 2 subjects had ‘poor’ control (median Phe level >1000 mol/L). All subjects were instructed to remain on their usual Phe restricted diet. For the phases without medical product advice was given on energy supplements (Polyjoule™ or Duocal™) needed to replace energy intake usually obtained from the medical product. The subjects were asked to complete a three day food diary during each phase in order to assess intake of dietary protein, Phe and other LNAA. Diet records also included medical product intake. Diet records were analysed using SERVE version 4.1.03 for nutrient and amino acid intake using Australian and UK amino acid analysis [16,17]. Where values for amino acids were unavailable, these were extrapolated from the major or similar ingredient.

Neuropsychological assessment

Baseline intellectual functioning was assessed on the Wechsler Abbreviated Scale of Intelligence [18] before commencement of treatment phases. At the end of each of the four treatment phases, subjects were administered a battery of neuropsychological tests to assess specific components of attention and executive function. The battery included the Continuous Performance Test-11 (CPT-II) [19]; subtests from the Components of attention and executive function. The battery included the Bridge Neuropsychological Test Automated Battery (CANTAB) [20] and Continuous Performance Test-11 (CPT-II) [19]; subtests from the Components of attention and executive function. The battery included the Bridge Neuropsychological Test Automated Battery (CANTAB) [20] and Continuous Performance Test-11 (CPT-II) [19]; subtests from the Components of attention and executive function. The battery included the Components of attention and executive function. The battery included the Components of attention and executive function. The battery included the Components of attention and executive function.

Measurement of brain Phe levels by magnetic resonance spectroscopy

All images and spectra were acquired with a Philips 1.5 T ACS-NT Gyroscan spectrometer and a quadrature head coil. The region of interest was localised from fast T2 weighted Turbo Spin Echo (TSE) images acquired in three planes: repetition time (TR) 2500, echo time (TE) 105 ms, Turbo factor 19, slice thickness 5 mm, 1.5 mm gap (45–60 s per sequence). The ROI (70 × 70 × 20 mm slab) was placed parallel to the AC–PC line at the superior margins of the body of the lateral ventricles and was adjusted so as not to include the calvarium.

All proton magnetic resonance spectra were acquired using the PRESS pulse sequence. A spectrum was acquired to measure the resonances derived from N-acetylaspartate (NAA), a marker of neuronal integrity; a composite peak arising from glycerophosphocholine, phosphocholine with a small contribution from free choline (Cho); and a composite peak arising from the N-methyl resonances of creatine and phosphocreatine (Cre) comprising the sum of 64 transients (TR 2 s, TE 136 ms across 1024 data points. A shorter echo spectrum was then obtained for quantification of the Phe resonance (TR 2 s, TE 20 ms across 1024 data points). A single scan spectrum was acquired without water suppression for use as an internal standard.

All images and spectra were stored by patient code and de-identified. They were all processed by an operator blind to the subject’s phase of the study.

Spectra were processed using MRUI (version 2.1; [23]). Quantification of reconstructed signals was performed in the time domain. AMARES, a nonlinear least squares fitting algorithm [24] was used to fit exponentially damped sinusoids (corresponding to Lorentzian lineshapes in the frequency domain) to resonance frequencies assigned to NA, Cho and Cre following removal of the residual water signal with HLSVD [25]. A Lorentzian lineshape was fitted to the resonance arising from water in the spectrum acquired without water suppression. Results are expressed as peak ratios and also as concentrations relative to the water resonance (in arbitrary units, without correction for relaxation or number of scans).

Brain Phe was quantified according to the method described by Möller [26].

Plasma amino acid quantitation

Plasma Phe levels were also obtained at the completion of each phase as part of a full plasma amino acid quantitation using ion-exchange chromatography and ninhydrin post-column derivatization. Blood was taken in late afternoon, 0.5–2 h before measurement of brain Phe levels, with no food, medical product or LNAA supplement in the intervening time.

Statistical analysis for metabolic measurements

Measurements of brain Phe (and the other brain metabolites), plasma Phe, and the brain/plasma Phe ratio were compared between phases using the Wilcoxon’s rank order test (non-parametric tests were used as the sample size was small and not all of the measurements were normally distributed).

Statistical analysis for neuropsychological variables

The impact of treatment on neuropsychological functioning/psychological status was analysed using repeated measures ANOVA and paired tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Measures</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Attention, Reaction time, Response inhibition</td>
<td>The ability to concentrate and attend to information over a length of time, Ability to inhibit an unwanted automatic response</td>
</tr>
<tr>
<td>D-KEFS</td>
<td>Verbal fluency, design fluency, Color/word interference</td>
<td>Ability to generate and retrieve information from mind, Ability to keep track of output</td>
</tr>
<tr>
<td></td>
<td>Generativity, Self monitoring, Cognitive flexibility</td>
<td>The ability to shift between two lines of thought</td>
</tr>
<tr>
<td>CANTAB</td>
<td>Stockings of Cambridge, Spatial span, Spatial working memory</td>
<td>Planning, Immediate span, Working memory</td>
</tr>
<tr>
<td></td>
<td>Planning, Immediate span, Working memory</td>
<td>Amount of visual information that can be held in mind briefly, Manipulation of information in mind</td>
</tr>
</tbody>
</table>
sample t tests. Spearman correlations were undertaken to investigate the relationship between brain Phe, plasma Phe and neuropsychological functioning/psychological status at each treatment phase.

Results

Overall compliance for consumption of the prescribed amount of active LNAA tablets was very good. In phase 1, the average number of prescribed tablets taken was 98%, and in phase 3 the average number of prescribed tablets taken was 94%. Two of the subjects in phase 3 did not return their remaining tablets, hence compliance for these subjects was not assessed, and it was assumed that they had consumed all tablets prescribed.

The data provided here represent dietary information, brain Phe levels, plasma Phe levels, and neuropsychological studies of all 16 patients.

Dietary analysis

Subject 6 did not submit food records in phases 2, 3 and 4 and subject 10 failed to submit a food record in phase 4, hence these two subjects were excluded from all dietary analyses.

Dietary Phe intake in phase 1 was significantly different when compared to dietary Phe intake in phase 2 (p = 0.04) and phase 4 (p = 0.004) (by Wilcoxon’s test) (see Table 3). Re-analysis of results using the Goldberg cut-off for identifying diet reports of poor validity [27] did not result in a significant difference. Weight did not change significantly across phases.

As expected, dietary analysis showed that both total protein and LNAA intake was highest in phase 1, followed by phase 2, then phase 3, and lowest in phase 4 (Table 3).

Magnetic resonance spectroscopy

There was no significant difference in brain Phe between the phases (data not shown) and the range of brain Phe measurements was small (176–365 μmol/L). There was no correlation between plasma and brain Phe when the plasma Phe was <1200 μmol/L, whilst for samples in phase 4 of the study where the plasma Phe was 1200 μmol/L or more there was a positive correlation (Spearman’s ρ = 0.90, p = 0.04), although there were only five data points in the latter group. Therefore, further analyses were not undertaken examining for correlations between brain metabolites and blood or neuropsychological measures.

Biochemical studies

Results for plasma Phe and the plasma Phe/Tyrosine (Tyr) ratio at the end of each phase are given in Fig. 1 and Table 3. Wilcoxon’s rank order test was used to determine if there were any significant differences between phases. No significant correlations were found when plasma Phe was compared directly with total LNAA intake, or dietary Phe intake, in any of the phases. Plasma Phe increased from phase 1 through to phase 4 (Fig. 1a). Thus, higher plasma Phe levels were found in the phases with the lowest LNAA intake. There were significant differences in plasma Phe between phase 3 and 4 (p = 0.001), between phase 1 and 3 (p = 0.001), between phase 1 and 4 (p < 0.0005), between phase 2 and 4 (p = 0.001), and between phase 2 and 3 (p = 0.023). There was no significant difference between phase 1 and 2 (p = 0.22), however, plasma Phe was reduced in most subjects (9 of 16) by an average of 24.9% during the active phase (phase 1) for this phase comparison.

The plasma Phe/Tyr ratio increased from phase 1 through to phase 4 (Fig. 1b). However, no significant correlations were found when the plasma Phe/Tyr ratio was compared directly with total dietary LNAA intake, or dietary Phe intake. There were significant differences between phase 1 and 2 (p = 0.017), between phase 3 and 4 (p = 0.001), between phase 1 and 3 (p = 0.020), between phase 1 and 4 (p < 0.001), and between phase 2 and 4 (p < 0.001). There was no significant difference between phases 2 and 3 (p = 0.23).

We compared the plasma LNAA levels for isoleucine, leucine, threonine, tyrosine, methionine, valine, lysine and histidine in each of the phases (data not shown). For most

<table>
<thead>
<tr>
<th>Phase</th>
<th>Medical product/active</th>
<th>Medical product/placebo</th>
<th>No medical product/active</th>
<th>No medical product/placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phe intake mg/kg/day</td>
<td>18.6 (5.3, 27.9)</td>
<td>18.5 (6.4, 43.9)</td>
<td>17.5 (4.5, 29.7)</td>
<td>21.8 (6.2, 27.9)</td>
</tr>
<tr>
<td>Protein from food g/kg/day</td>
<td>0.41 (0.13, 0.64)</td>
<td>0.40 (0.14, 0.94)</td>
<td>0.39 (0.12, 0.68)</td>
<td>0.51 (0.17, 0.62)</td>
</tr>
<tr>
<td>Protein from medical product g/kg/day</td>
<td>0.95 (0.13, 1.41)</td>
<td>0.94 (0.13, 1.45)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Protein from LNAA supplement g/kg/day</td>
<td>0.25 (0.18, 0.25)</td>
<td>0</td>
<td>0.25 (0.18, 0.25)</td>
<td>0</td>
</tr>
<tr>
<td>Protein total g/kg/day</td>
<td>1.62 (0.96, 2.10)</td>
<td>1.43 (0.88, 1.85)</td>
<td>0.63 (0.34, 0.93)</td>
<td>0.51 (0.17, 0.62)</td>
</tr>
<tr>
<td>LNAA from food g/kg/day</td>
<td>0.13 (0.04, 0.21)</td>
<td>0.14 (0.05, 0.32)</td>
<td>0.11 (0.04, 0.21)</td>
<td>0.15 (0.05, 0.21)</td>
</tr>
<tr>
<td>LNAA from medical product g/kg/day</td>
<td>0.53 (0.08, 0.88)</td>
<td>0.55 (0.08, 0.91)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LNAA from supplement g/kg/day</td>
<td>0.25 (0.18, 0.26)</td>
<td>0</td>
<td>0.25 (0.19, 0.25)</td>
<td>0</td>
</tr>
<tr>
<td>LNAA total g/kg/day</td>
<td>0.90 (0.53, 1.27)</td>
<td>0.75 (0.32, 1.05)</td>
<td>0.35 (0.24, 0.46)</td>
<td>0.15 (0.05, 0.21)</td>
</tr>
<tr>
<td>Plasma Phe (μmol/L)</td>
<td>639 (149, 1044)</td>
<td>734 (19, 1231)</td>
<td>958 (553, 1500)</td>
<td>1180 (641, 1744)</td>
</tr>
<tr>
<td>Plasma Phe/Tyr ratio</td>
<td>10 (1.2, 17.9)</td>
<td>14 (0.2, 27.5)</td>
<td>18 (8.6, 36.6)</td>
<td>30 (11.9, 52.1)</td>
</tr>
</tbody>
</table>
of the plasma LNAAs, levels were highest in phase 1 and progressively fell through to phase 4, reflecting intake. An exception was methionine, and to a lesser extent, histidine, which were highest in phase 3. Compared to the other LNAAs, methionine is present in the lowest quantities in all of the medical products our subjects were usually taking (XP Maxamum™, Phlexy 10™, PKU Express™). In fact, the average percent boost of methionine from the LNAA supplement over the methionine in the usual medical product for all subjects was 267%. Similarly, the percent boost provided by the LNAA supplement for histidine was 127%.

Neuropsychological testing results

The mean overall intellectual functioning for participants was rated average \((m = 101, SD = 16)\) with a range from superior ability to moderate intellectual impairment.

Paired sample \(t\) tests between phases revealed better performances on measures of verbal generativity \((t = 2.657, p = 0.018)\) in phase 3 as compared to phase 4. Significantly better verbal self-monitoring \((t = 2.179, p = 0.046)\) was found in phase 3 as compared to phase 1.

Spearman correlations were undertaken to investigate the relationship between plasma Phe and neuropsychological functioning/psychological status at each treatment phase. Analysis of the association between the neuropsychological measures and plasma Phe at each phase revealed several significant negative correlations. In phase 1, significant negative correlations were obtained between plasma Phe and semantic verbal fluency (VF-Category; \(rs = -0.525, p = 0.018\)). In phase 2, plasma Phe and inattention was significantly correlated (CPT-Errors, \(rs = -0.441, p = 0.044\)). In phase 3 a negative correlation between spatial working memory and plasma Phe was obtained (SWM, \(rs = -0.464, p = 0.035\)). In phase 4, no significant correlations were obtained.

The plasma Phe and neuropsychological and psychological measures were pooled across phases to obtain a mean level of performance and plasma Phe. Spearman correlations were undertaken to investigate the relationship between mean plasma Phe and mean neuropsychological functioning/psychological status. Statistically significant negative correlations were obtained between plasma Phe and verbal generativity (VF-Letters; \(rs = -0.465, p = 0.035\)) and non-verbal self-monitoring (DF-reps, \(rs = -0.488, p = 0.027\)).

Further investigations showed better performances on attention measures when subjects were on standard medical product (phase 1 and 2) in comparison to off standard medical product (phase 3 and 4) \((F = 23.64, p = 0.000)\). Higher levels of anxiety symptoms were also reported when on LNAAs \((F = 5.2, p = 0.039)\) (phase 1 and 3 compared to phase 2 and 4).

Discussion

Previous studies have suggested that Phe transport from the plasma into the brain is via the neutral amino acid transporter and is driven by a concentration gradient [28]. This transport is competitively inhibited by the presence of other LNAAs in the plasma [12]. In addition, the efficiency of this transport system appears to vary between individuals. This offers an explanation to the surprising observation reported by others that there exist certain ‘exceptional individuals’ who are able to maintain relatively low levels of brain Phe and normal cognitive function despite persistently high plasma Phe levels [12, 28, 29].

Our study consisted of four phases with varying LNAAs intake. As expected, the dietary analysis showed that both total protein and LNAAs intake was highest in phase 1 (on usual medical product and LNAAs supplements), followed by phase 2 (on usual medical product, no LNAAs supplements), then phase 3 (off usual medical product, on LNAAs supplements), and lowest in phase 4 (off usual medical product, no LNAAs supplements). Compliance for consuming the LNAAs supplement was good. Phe intake from regu-
lar food was significantly different between phase 1 and 2, and between phase 1 and 4. While there may well be variation in daily Phe intake, assessment of intake during this study was also limited by the assessment of 3 day food records kept at varying times within the 2 week phase, and the use of incomplete amino acid analysis data.

We were unable to demonstrate a positive correlation between plasma and brain Phe when the plasma Phe level was under 1200 μmol/L. There was a positive correlation when the plasma Phe was 1200 μmol/L or more (all samples were collected during phase 4 of the study), but it is difficult to draw any firm conclusions given the small number of samples with these higher values in our study. These findings are in accord with the findings of Moats et al. [28], who found a poor correlation between blood and brain Phe levels.

In our study plasma Phe and plasma Phe/Tyr ratio increased from phase 1 through to phase 4 as the LNAA intake decreased. The highest plasma Phe levels occurred in phase 4 which cannot be accounted for by differences in Phe intake. This has been recognized in other patients whose plasma levels increase when they are not taking their medical product. A possible mechanism for this may be that supplementary dietary LNAA may compete with Phe for transport across the intestinal mucosa, as a recent in vitro study using human intestinal epithelial Caco-2 cells showed that apical to basolateral transport of phenylalanine competes with LNAAAs [30]. This hypothesis is supported by a recent study by Matalon et al., where LNAA supplementation led to a fall in blood Phe by up to 55%, depending on the dosage used [31].

Interestingly, our results suggested that LNAA supplementation alone had a positive effect on executive functioning, specifically, verbal generativity, cognitive flexibility and self-monitoring whilst standard treatment (medical products) was associated with positive outcome on measures of attention. However, our studies also indicated that anxiety levels were higher when participants were on LNAA supplementation. Overall, these findings suggest that at a group level LNAA supplementation has some beneficial effect on specific cognitive functioning, although our studies also suggest that there is considerable individual variation.

In keeping with previous literature, negative correlations were found between plasma Phe levels and cognition. In particular higher plasma levels were associated with lower performances on measures of executive functioning including verbal generativity, self-monitoring, response inhibition and working memory. These findings support previous findings of the detrimental effect of high plasma Phe levels on cognition.

In summary, there was a trend to a lowering of plasma Phe levels, with a higher intake of LNAA. This may be a result of competitive inhibition of Phe with LNAAAs at the intestinal mucosa. These findings suggest that the decision for using LNAA supplements will need to be individualized, and may be of most benefit in those who are unable to comply with their medical product.

Acknowledgments

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References


