

Large neutral amino acids in the treatment of PKU: from theory to practice

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Abstract Notwithstanding the success of the traditional dietary phenylalanine restriction treatment in phenylketonuria (PKU), the use of large neutral amino acid (LNAA) supplementation rather than phenylalanine restriction has been suggested. This treatment modality deserves attention as it might improve cognitive outcome and quality of life in patients with PKU. Following various theories about the pathogenesis of cognitive dysfunction in PKU, LNAA supplementation may have multiple treatment targets: a specific reduction in brain phenylalanine concentrations, a reduction in blood (and consequently brain) phenylalanine concentrations, an increase in brain neurotransmitter concentrations, and an increase in brain essential amino acid concentrations. These treatment targets imply different treatment regimes. This review summarizes the treatment targets and the treatment regimens of LNAA supplementation and discusses the differences in LNAA intake between the classical dietary phenylalanine-restricted diet and several LNAA treatment forms.

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Abbreviations

CSF	Cerebrospinal fluid
LNAA	Large neutral amino acids
PAH	Phenylalanine hydroxylase
Phe	Phenylalanine
PKU	Phenylketonuria

Introduction

In phenylketonuria (PKU, OMIM 261600), dietary restriction of phenylalanine (Phe) has been the cornerstone of treatment for over 50 years. The result of dietary treatment is a near normal cognitive outcome, although mild neuropsychological disturbances may still occur (Christ et al. 2010). Large neutral amino acids (LNAAs) have been suggested as an alternative treatment to further improve outcome. Possible LNAA treatment targets include reduction of brain Phe concentrations (Berry et al. 1982; Jordan et al. 1985; Pietz et al. 1999), reduction of blood Phe concentrations (Matalon et al. 2006), augmentation of cerebral neurotransmitter synthesis (Lou et al. 1985; Güttler and Lou 1986; Lou et al. 1987; Lykkelund et al. 1988), and/or elevation of brain non-Phe LNAA concentrations (Van Spronsen et al. 2009). In this article, we summarize the reports of the clinical trials of LNAAs and the rationales behind the use of LNAAs.

Apart from Phe, LNAAs include tyrosine, tryptophan, threonine, methionine, valine, isoleucine, leucine, and histidine (Van Spronsen et al. 2009). In healthy individuals, all of these except tyrosine are essential amino acids. In patients with PKU, tyrosine has become an essential amino acid. LNAA treatment as an alternative to dietary Phe restriction was suggested as early as 1948 (Christensen et

al. 1948) and first studied in rats in 1976 (Andersen and Avins 1976). Since then, different combinations of LNAAs have been designed, based on different rationales and treatment targets. Some LNAA combinations contain arginine and/or lysine, neither of which is an LNAA.

This paper reviews different treatment regimes and different treatment rationales in LNAA supplementation.

Rationale A: LNAA supplementation to decrease cerebral Phe concentrations

The underlying rationale for this therapeutic strategy is that elevated brain Phe concentrations are considered to be neurotoxic. Because all LNAAs share a common transport system in order to enter the brain, and high plasma concentrations of LNAAs may block the transport of Phe into the brain (Pardridge 1998), increasing blood LNAA concentrations may reduce uptake of Phe into the brain. This hypothesis was first studied in rats with experimental hyperphenylalaninemia. LNAA-treated hyperphenylalaninemic rats were shown to have significantly reduced brain Phe concentrations compared to untreated hyperphenylalaninemic control rats, at similar blood Phe concentrations (Andersen and Avins 1976). Later studies in PKU patients showed that supplementation with valine, isoleucine, and leucine resulted in slightly improved neuropsychological function in patients with PKU (Jordan et al. 1985; Berry et al. 1990). More recent studies included the administration of all LNAAs. Pietz et al. (1999) and Moats et al. (2003) showed that oral LNAA supplementation reduced brain Phe concentrations, and improved neurophysiological and neuropsychological functioning (Pietz et al. 1999; Moats et al. 2003; Schindeler et al. 2007). Differences in outcome may be related to composition, dosing, route of administration, and duration of the supplementation period.

Rationale B: tyrosine and/or tryptophan supplementation to increase cerebral neurotransmitter synthesis

The rationale for this therapeutic strategy is that high plasma Phe concentrations result in decreased brain neurotransmitter concentrations. This is reflected by reduced brain neurotransmitter concentrations in the PKU mouse brain (Puglisi-Allegra et al. 2000; Pascucci et al. 2002, 2008, 2009), and by reduced concentrations of dopamine and serotonin and their metabolites in PKU patients, both in cerebrospinal fluid (CSF) (Butler et al. 1981; Lou et al. 1985; Burlina et al. 2000), and in autopsied brain tissue (McKean 1972). In PKU patients

with an unrestricted natural protein intake, tyrosine and tryptophan supplementation have been shown to improve neurotransmitter metabolism, reaction time, and vigilance (Güttler and Lou 1986; Lou et al. 1987; Lykkelund et al. 1988), suggesting that dietary treatment could be replaced by a combination of tyrosine and tryptophan. Further support for such a treatment strategy was based on the theory of prefrontal lobe dysfunction (Diamond et al. 1994). This theory presumes that the prefrontal cortex is most affected by dopamine depletion, because dopaminergic neurons innervating the prefrontal cortex have relatively high levels of activity and higher dopamine turnover, inducing dopamine-dependency. Following these lines of consideration, large doses of tyrosine or L-dopa were expected to have a positive effect. However, later studies with large doses of tyrosine or L-dopa did not show positive results (Lou 1994; Mazzocco et al. 1992; Pietz et al. 1995; Smith et al. 1998; Ullrich et al. 1996).

Rationale C: LNAA supplementation to decrease blood Phe concentrations

This therapeutic strategy of supplementing LNAA is based on the rationale that LNAA transport not only occurs at the blood–brain barrier (BBB), but also at the gut–blood barrier. After performing studies in mice, Matalon et al. (2003) performed an open and a double-blinded trial in patients, who received LNAAs three times daily with meals, while patients' regular diet was unchanged (Matalon et al. 2006, 2007). A decrease in blood Phe concentrations up to 50% of initial values was found on LNAA supplementation of 0.5–1.0 g kg⁻¹ day⁻¹ (Matalon et al. 2006, 2007). This suggests that LNAA supplementation superimposed on regular dietary treatment may reduce Phe absorption in the gastrointestinal tract. If reduction in blood Phe concentrations indeed results from reduced Phe absorption, supplementation of all LNAAs at this dosage may not be required, as supplementation with threonine up to 50 mg/kg is reported to be sufficient to reduce blood Phe concentration by 20–50% (Sanjurjo et al. 2003). In addition, the reduction of blood Phe concentrations following LNAA supplementation may at least partly result from increased protein synthesis resulting from increased essential amino acid availability, in case of essential amino acid deficiency. However, it is largely unknown whether the patients studied had essential amino acid deficiencies (due to insufficient intake of natural protein and/or protein substitute), as so far, none of the clinical studies on the effects of LNAA supplementation quantified the amount of natural protein and protein substitute intake patients used. Finally, reduced blood Phe concentrations on LNAA supplementation may just be a matter of timing

of blood sampling, as suggested by Prof. Bachmann (personal communication).

Rationale D: LNAA supplementation to increase cerebral amino acid concentrations

Reduced brain LNAA concentrations have been reported in PKU mice (Smith and Kang 2000; Pascucci et al. 2002, 2008). In autopsied brain tissue of PKU patients, McKean reported reduced tyrosine concentrations (McKean 1972). Restoring reduced brain LNAA concentrations in PKU may improve cognitive outcome. The rationale for LNAA supplementation to increase cerebral LNAA concentrations is, again, that LNAAs share the same transport system as Phe for entering the brain. Where rationale A hypothesizes that it is important to decrease the brain Phe concentration, rationale D hypothesizes that a deficiency in any essential amino acid in the brain may affect brain (protein) metabolism. Consequently, rationale D focuses on the effect of LNAA treatment on brain LNAA concentrations, rather than on (a decrease in) brain Phe concentrations. Hoeksma et al. (2009) showed that a significant negative relationship exists between plasma Phe concentration and cerebral protein synthesis in patients with PKU. However, this finding does not differentiate between the influence of elevated brain Phe concentrations and reduced brain non-Phe LNAA concentrations on cerebral protein synthesis.

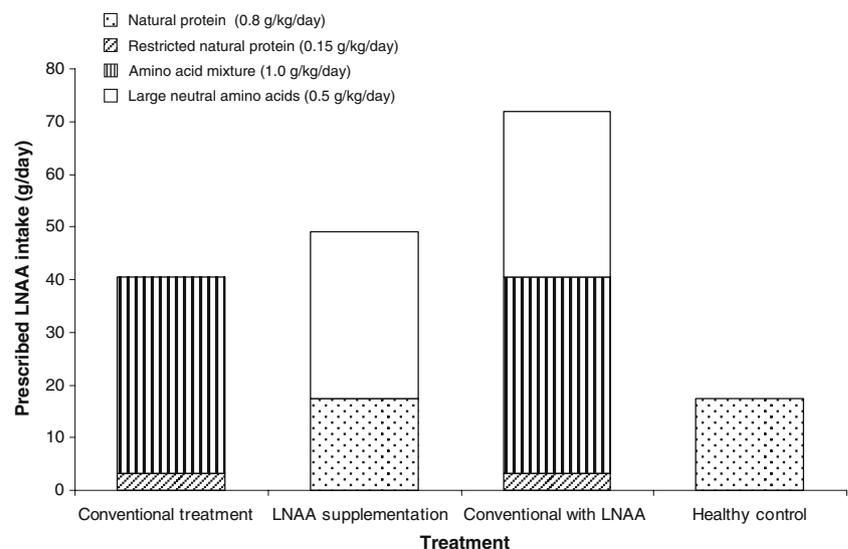
Rationale E: comparison of LNAA intake in LNAA treatment and present dietary treatment

Recent trials with LNAA supplements in PKU patients include LNAA alone (Pietz et al. 1999), LNAA with extra

lysine and/or arginine (Koch et al. 2003; Moats et al. 2003; Matalon et al. 2006, 2007; Schindeler et al. 2007), or only threonine (Sanjurjo et al. 2003). Whatever combination of amino acids is given, LNAA treatment strategies start with a more or less normal (i.e., unrestricted) intake of natural protein. The response of blood Phe concentrations to LNAA treatment (Pietz et al. 1999; Koch et al. 2003; Moats et al. 2003; Matalon et al. 2006, 2007; Schindeler et al. 2007) is comparable to the response of blood Phe concentrations to the protein substitutes in the traditional dietary treatment (MacDonald et al. 1996; Crone et al. 2005).

To illustrate treatment-dependent differences in LNAA intake, we calculated prescribed LNAA intake for several treatment regimes, based on an adult PKU patient with a body weight of 70 kg (Fig. 1). In Fig. 1, prescribed LNAA intake is compared among four different diets: (1) conventional dietary PKU treatment consisting of Phe-restriction combined with synthetic amino acid mixtures, (2) LNAA supplementation ($0.5 \text{ g kg}^{-1} \text{ day}^{-1}$) with natural protein intake at $0.8 \text{ g kg}^{-1} \text{ day}^{-1}$, the recommended daily allowance (RDA) (National Research Council 1989), (3) LNAA supplementation combined with conventional dietary treatment, (4) RDA of protein of healthy adults. For calculation of LNAA content of synthetic amino acid mixtures (treatment 1), the mean of the following 14 amino acid mixtures was used: PKU3[®] (Milupa), PKU3advanta[®] (Milupa), XP Maxamum[®] (SHS), Lowphlex Powder[®] (SHS), Phlexy-10 drinkmix[®] (SHS), Phlexy-10 tablets[®] (SHS), PK Aid-4[®] (SHS), Aminogran[®] (UCB Pharma), PKU Express Powder[®] (VitaFlo), Phenex-2[®] (Ross), Xphe advance[®] (Metax), Easiphen[®] (SHS), PKU Express Liquid[®] (VitaFlo), Lophlex Liquid[®] (SHS). Regarding LNAA supplementation (treatments 2 and 3), a dose of $0.5 \text{ g kg}^{-1} \text{ day}^{-1}$ is used, based on several recent trials following the work of Moats et al. (2003) and Koch et al. (2003). Prescribed

Fig. 1 Prescribed large neutral amino acids intake (g/day) on different treatment regimes



LNAA intake of these treatments was calculated as the mean of Lanaflex® (SHS international) and NeoPhe® (Solace Nutrition). The dietary regimen of LNAA supplementation combined with conventional dietary treatment (treatment 3) reflects the regimen studied by Matalon et al. (2006, 2007).

Several assumptions underlie the calculated values. First, the dose of amino acid mixture in conventional treatment is set at $1.0 \text{ g kg}^{-1} \text{ day}^{-1}$ rather than the RDA ($0.8 \text{ g kg}^{-1} \text{ day}^{-1}$), correcting for the assumed 20% of the mixture that is not absorbed in the gastrointestinal tract. Second, in conventional treatment, LNAA intake resulting from natural protein intake is not taken into account, as the natural protein in this treatment is assumed to be of relatively low nutritional value. However, the distinction between protein of relatively low and high nutritional value has not been applied to the prescribed LNAA intake at RDA of healthy controls, resulting in some inconsistencies.

Based on these calculated prescribed LNAA intakes, Fig. 1 demonstrates that LNAA intake in PKU is higher than in healthy controls, regardless of the specific treatment given. Moreover, LNAA intake on LNAA supplementation is higher than LNAA intake on conventional treatment. However, the difference in LNAA intake between these two treatment forms is small relative to the difference between conventional treatment and the dietary regimen studied by Matalon et al. Finally, LNAA intake on the treatment strategy studied by Matalon et al. clearly results in a higher LNAA intake than either conventional therapy or LNAA supplementation, and markedly exceeds LNAA intake of a healthy control.

When LNAA treatment is discussed, not only the dose but also the composition is important. It is remarkable that LNAA treatment would need the addition of the non-LNAA lysine and arginine. When the primary aim is to block the entrance of Phe into brain, this would favor LNAA supplements consisting of specific amino acids, such as leucine, isoleucine, and methionine, that are considered to be highly effective at decreasing the cerebral Phe concentration (Hargreaves and Pardridge 1998). Following that hypothesis, giving $0.5 \text{ g kg}^{-1} \text{ day}^{-1}$ of all LNAA together with lysine and arginine might be changed into $0.5 \text{ g kg}^{-1} \text{ day}^{-1}$ of leucine, isoleucine, and/or methionine (Hargreaves and Pardridge 1998).

When the primary aim is to increase the influx of tyrosine and tryptophan, this would favor the supplementation of only tyrosine and tryptophan to increase the synthesis of the neurotransmitters dopamine and serotonin in the brain. Following that hypothesis, giving $0.5 \text{ g kg}^{-1} \text{ day}^{-1}$ of all LNAA (with or without lysine and/or arginine) might be changed into $0.5 \text{ g kg}^{-1} \text{ day}^{-1}$ of tyrosine and tryptophan. This is clearly above the doses ever given to PKU patients so far (Lou et al. 1985, 1987; Güttler and Lou 1986; Lykkelund et al. 1988). When, however, increasing

the cerebral concentrations of all essential amino acids is the primary aim, all essential amino acids should be given in such a way that normal concentrations of all essential amino acids are achieved, taking the K_m of each amino acid into account.

Summary of current treatment strategies in LNAA supplementation

LNAA supplementation may have several treatment aims: reducing brain Phe concentrations, reducing plasma Phe concentrations, increasing cerebral neurotransmitter concentrations, and increasing cerebral essential amino acid concentrations. Although LNAA treatment in PKU was initially intended to be unrestricted natural protein intake combined with LNAA supplementation, it should be noted that not all authors studied LNAA supplementation in this manner. This deserves attention when interpreting the findings below.

First, LNAA supplementation has been found to reduce brain Phe concentrations in patients, even at mean plasma Phe concentrations $>1,000 \text{ } \mu\text{mol/L}$ (Pietz et al. 1999; Koch et al. 2003). Second, LNAA supplementation may reduce plasma Phe concentrations (Matalon et al. 2006, 2007; Sanjurjo et al. 2003), although not all authors report this effect (Pietz et al. 1999; Koch et al. 2003; Moats et al. 2003). Third, data suggest that supplementation with only tyrosine and tryptophan does not sufficiently correct biochemical and neuropsychological abnormalities. However, recent LNAA trials supplement LNAA at $0.5 \text{ g kg}^{-1} \text{ day}^{-1}$, a dose much higher than that studied for tyrosine and tryptophan supplementation. At this dose, the effect of LNAA supplementation on cerebral neurotransmitter concentrations is currently unknown. Fourth, LNAA supplementation combined with unrestricted natural protein intake has been suggested to increase cerebral essential amino acid concentrations. This hypothesis remains to be studied in future trials.

In conclusion, LNAA treatment is seen as an alternative to conventional dietary PKU treatment. Although usually considered to refer to a single specific treatment modality, this paper shows that LNAA treatment may refer to at least two different LNAA treatment strategies, i.e., natural protein intake at RDA with LNAA supplementation, and conventional dietary therapy combined with LNAA supplementation. In addition, LNAA treatment may refer to supplementation of single amino acids, such as tyrosine, tryptophan, and threonine. These differences in treatment strategies are based on clearly different theories regarding mechanism of action. Consequently, more in-depth studies are necessary to investigate the potential role, dose, and composition of LNAA in PKU treatment.

Competing interest Francjan J. van Spronsen is a member of the scientific advisory board of Merck Serono S.A. – Geneva, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany) regarding treatment for phenylketonuria and has received grants of Merck Serono. Margreet van Rijn is a member of the Merck Serono European Nutritionist Expert Panel in Phenylketonuria.

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