



The What, Why and How of Large Neutral Amino Acids

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The opinions reflected in this webinar are those of the speaker and independent of Nutricia North America



Objectives:

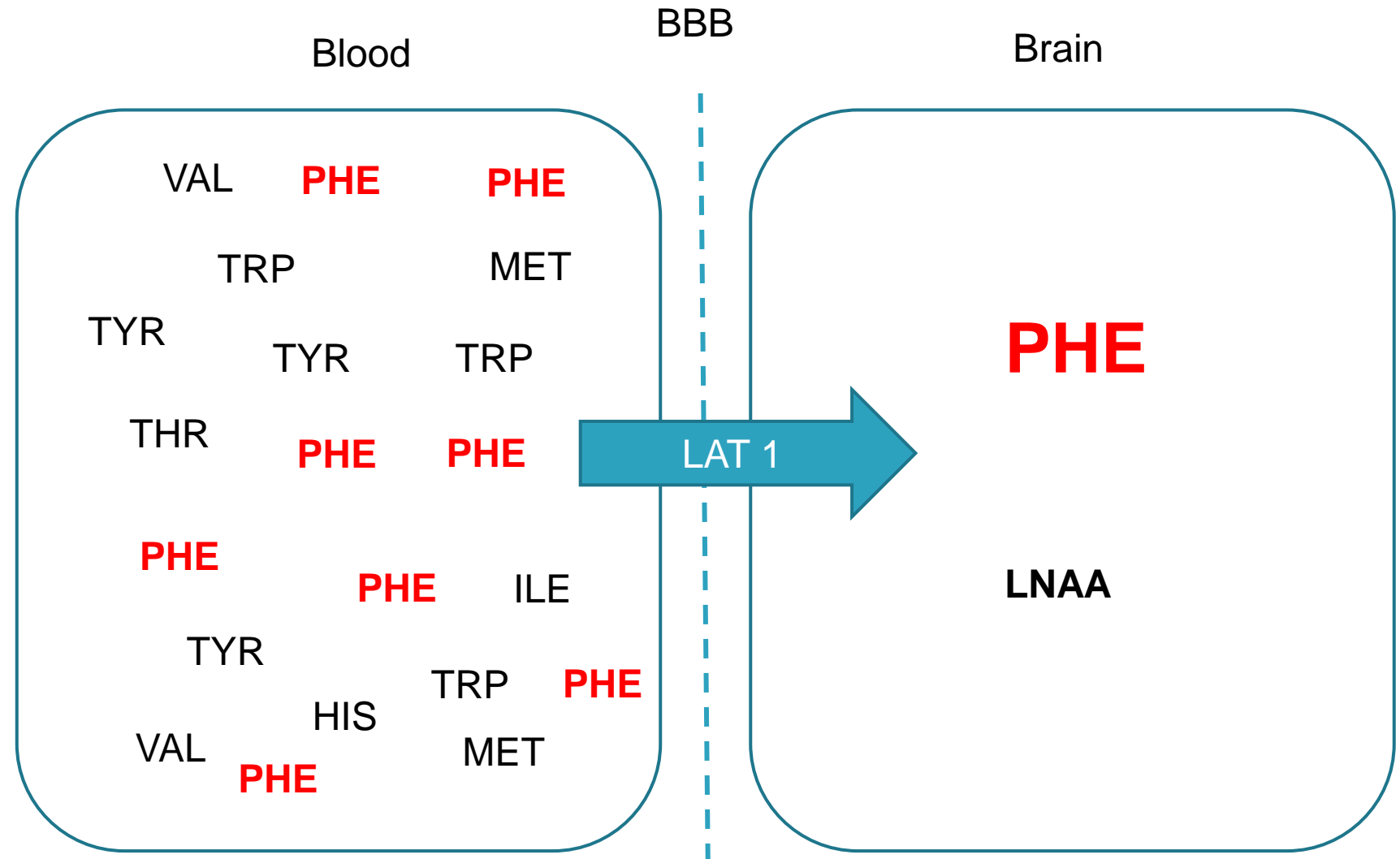
- Define large neutral amino acids (LNAA)
- Describe how LNAA are used in the nutrition management of PKU
- Describe LNAA use with other modalities; i.e., medical food products, saproterin dihydrochloride (BH₄)
- Demonstrate how to calculate dose and monitoring parameters

What are large neutral amino acids?

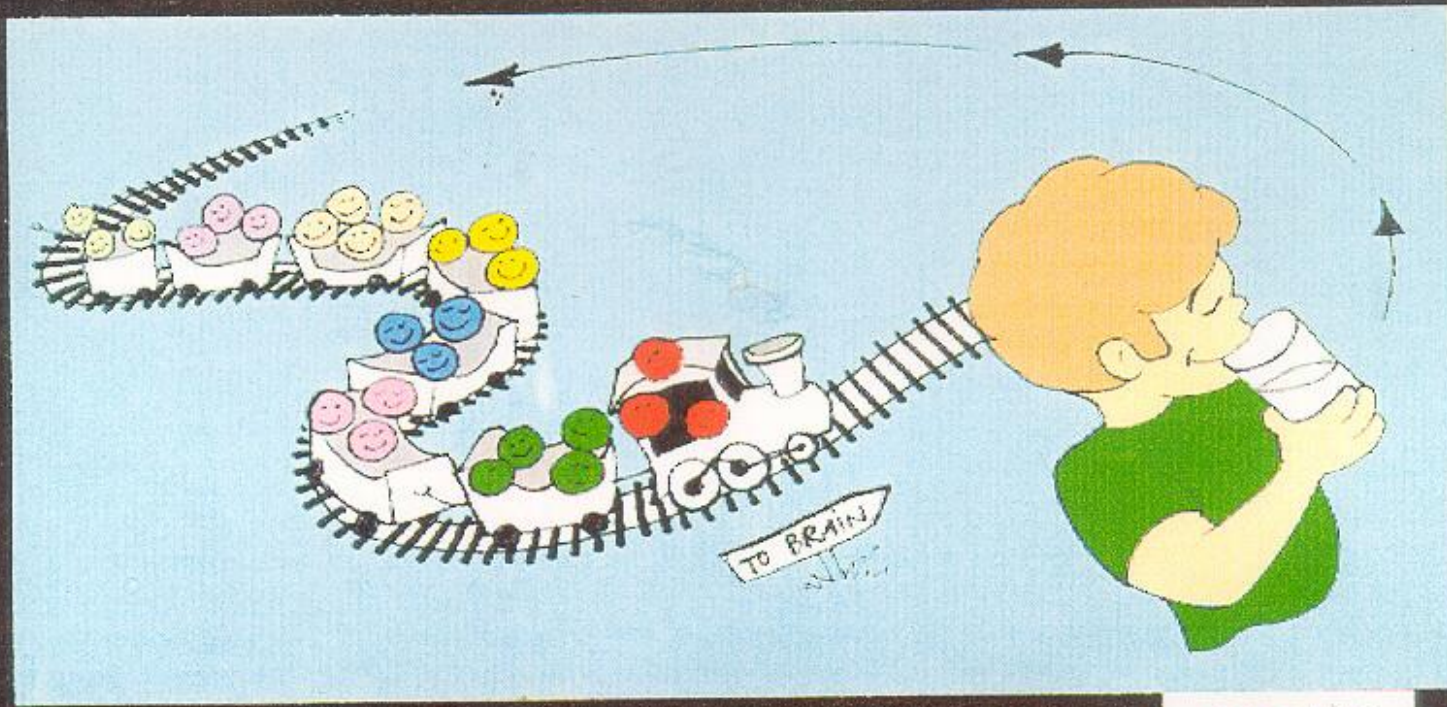
- Valine
- Methionine
- Isoleucine
- Leucine
- Histidine
- Threonine
- Arginine
- Tryptophan
- Tyrosine
- Phenylalanine

Mechanism of Action: LAT 1 Transporter

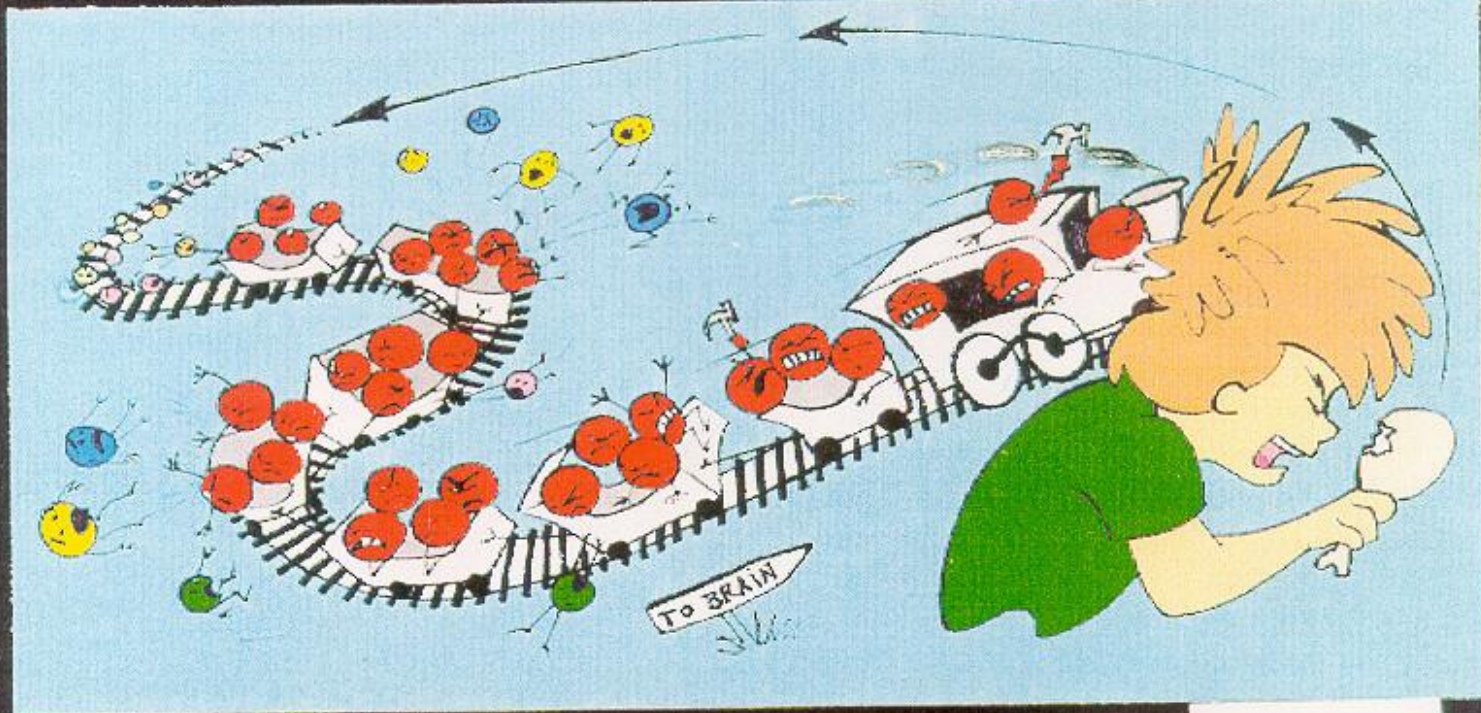
- High blood PHE and higher affinity of PHE to LAT 1 may lead to brain AA imbalances
- LNAA diet supplementation attempts to “out-crowd” PHE at BBB and increase influx of LNAA into the brain



The Amino Acid Train to the PKU Brain



ON DIET



OFF DIET

KEY:

PHE	MET	THR	LEU
HIST	VAL	ISO	TYR

LNAA have been researched for over 40 years

- Christensen, et al. Annu Rev Biochem. 1953;22:233-60.
 - Metabolism of aa and proteins
- Andersen, et al. Arch Neurol. 1976;33:684-6.
 - Lower brain phe by giving other LNAA (rat study)
- Pratt OE. J Ment Defic Res. 1980;24:203-17.
 - New approach to tx using LNAAA
- Lou, et al. Acta Paediatr Scand. 1987;76:560-5.
 - Increased vigilance and dopamine synthesis- tryrosine supplementation
- Berry, et al. Am J Dis Child. 1990;144:539-43.
 - Val, Ile, Leu
- Lou, et al. Acta Paediatr. 1994;83:1312-4.
 - Supplemented Prekunil- 92mg/kg try, 65mg/kg trp
- Pietz, et al. J Clin Invest. 1999;103:1169-78.
 - LNAA block phe in brain - MRS
- Pietz, et al. J Inherit Metab Dis. 2003;26:683-92.
 - Showing measurement of brain phe
- Koch, et al. Mol Genet Metab. 2003;79:110-3.
 - MRS lowering brain phe using Prekunil

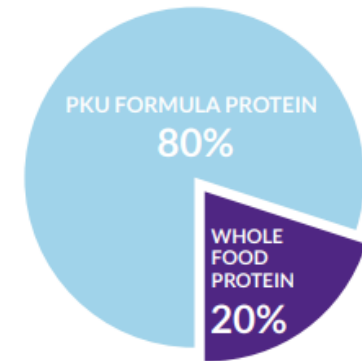
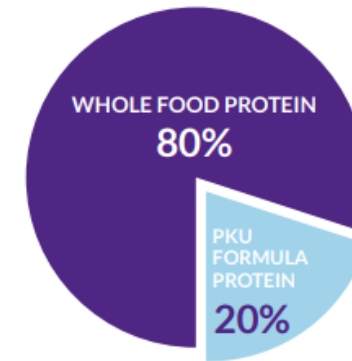
Cont.

- Matalon, et al. J Inherit Metab Dis. 2006;29:732-8.
 - Neophe-lowered blood phe
- Matalon, et al. J Inherit Metab Dis. 2007;30:153-8.
 - DB placebo- with LNAA 40% reduction in blood phe
- Schindeler, et al. Mol Genet Metab. 2007;91:48-54.
 - MRS and neuropsych measurements
- Yano, et al. J Pediatr. 2013;162:999-1003.
 - LNAA increases melatonin synthesis
- Yano, et al. J Pediatr. 2014;165:184-189.
 - Melatonin and dopamine as biomarkers
- van Vliet, et al. PLoS One. 2015;10(12).
 - LNAA supplementation exerts its effects through 3 synergistic mechanisms-mice – improves brain biochemistry-composition and dose need to be further optimized
- Yano, et al. PLoS One. 2016;11(8).
 - BH4 and LNAA
- Concolino, et al. Eur J Clin Nutr. 2017. 71:51-55.
 - (Italy) – 4 wks -LNAA tx new medical food, reduced blood phe decreased ratio ~40%

Whole protein intake can be increased with the LNAA approach

□ Traditional PKU Diet

- 80% protein from medical food
- 20% protein from whole protein



□ LNAA Diet

- 80% protein from whole protein
- 20% protein from medical food

LARGE NEUTRAL AMINO ACIDS (LNAA)

Began in Denmark in 1985

Who is the ideal patient for LNAA?

- Having difficulty taking medical food
- Struggling with a Phe-restricted diet
- Late diagnosed or never been on-diet
- No access to required low protein products

What do patients report?

- More energy
- More food choices
- Easy to swallow
- Feels like I am out of the “fog”
- “Happier”



**How do we know if the LNAA
approach works?**

Molecular Genetics and Metabolism

Large neutral amino acid therapy and phenylketonuria: A promising approach to treatment

Richard Koch,^a Kathryn D. Moseley,^a Shoji Yano,^a Marvin Nelson Jr.,^b
and Rex Moats^b

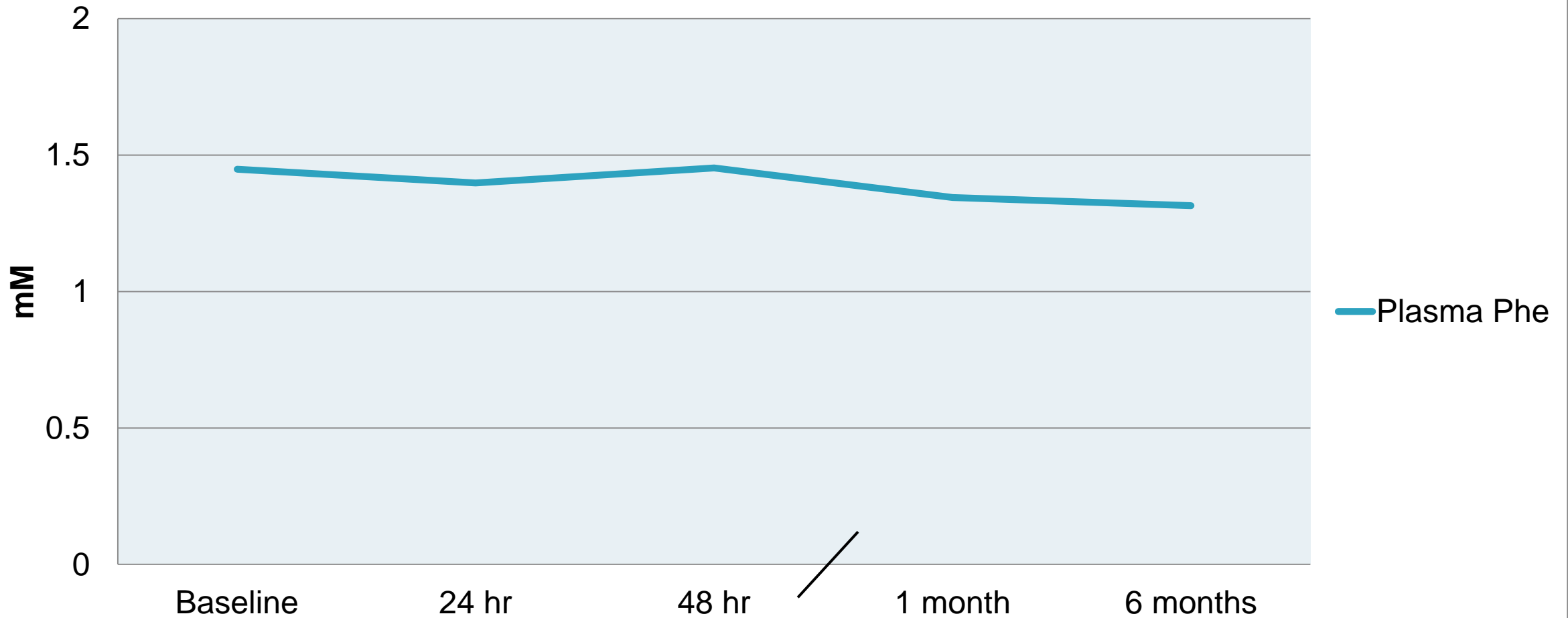
^aDivision of Medical Genetics and Radiology Department, MS#90, Childrens Hospital of Los Angeles, 4650 Sunset Boulevard, Los Angeles, CA 90027, USA

^bDepartment of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

2003

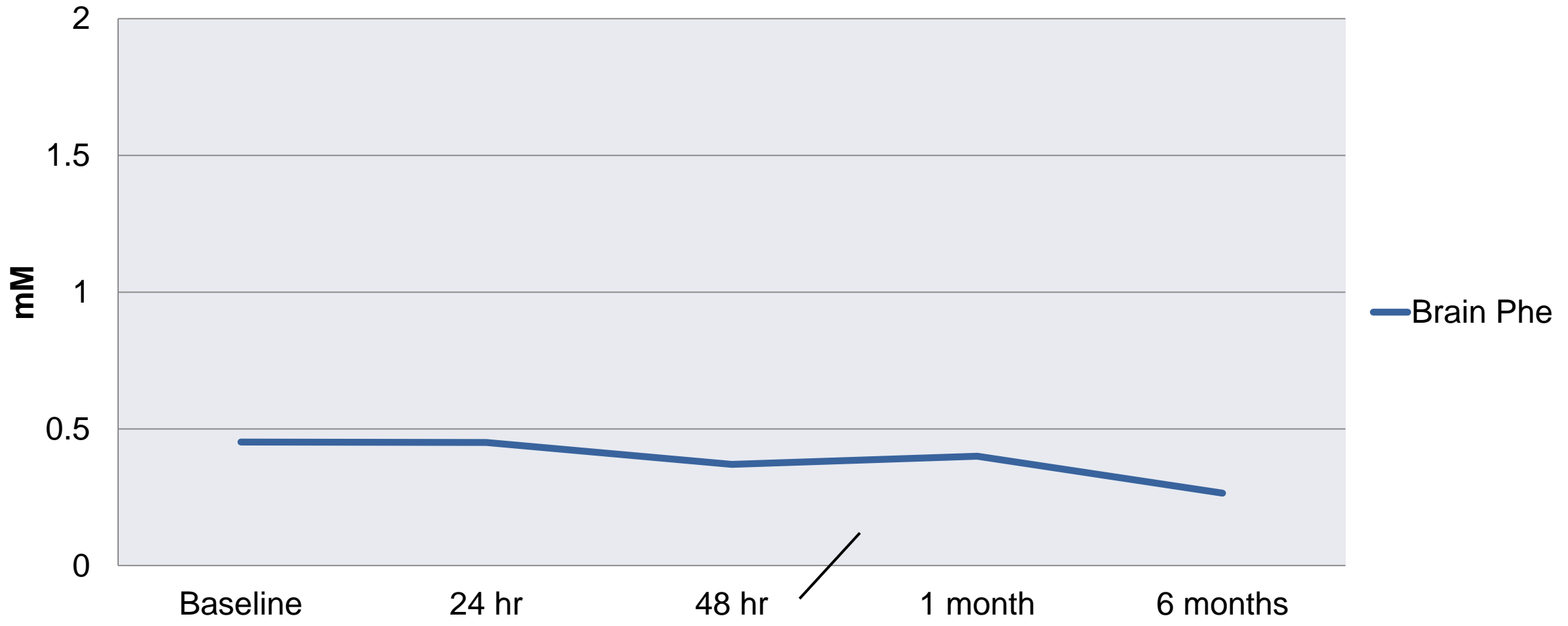
Plasma Phe levels remained the same over 6 months on LNAA

Mean Plasma Phe Over 6 Months



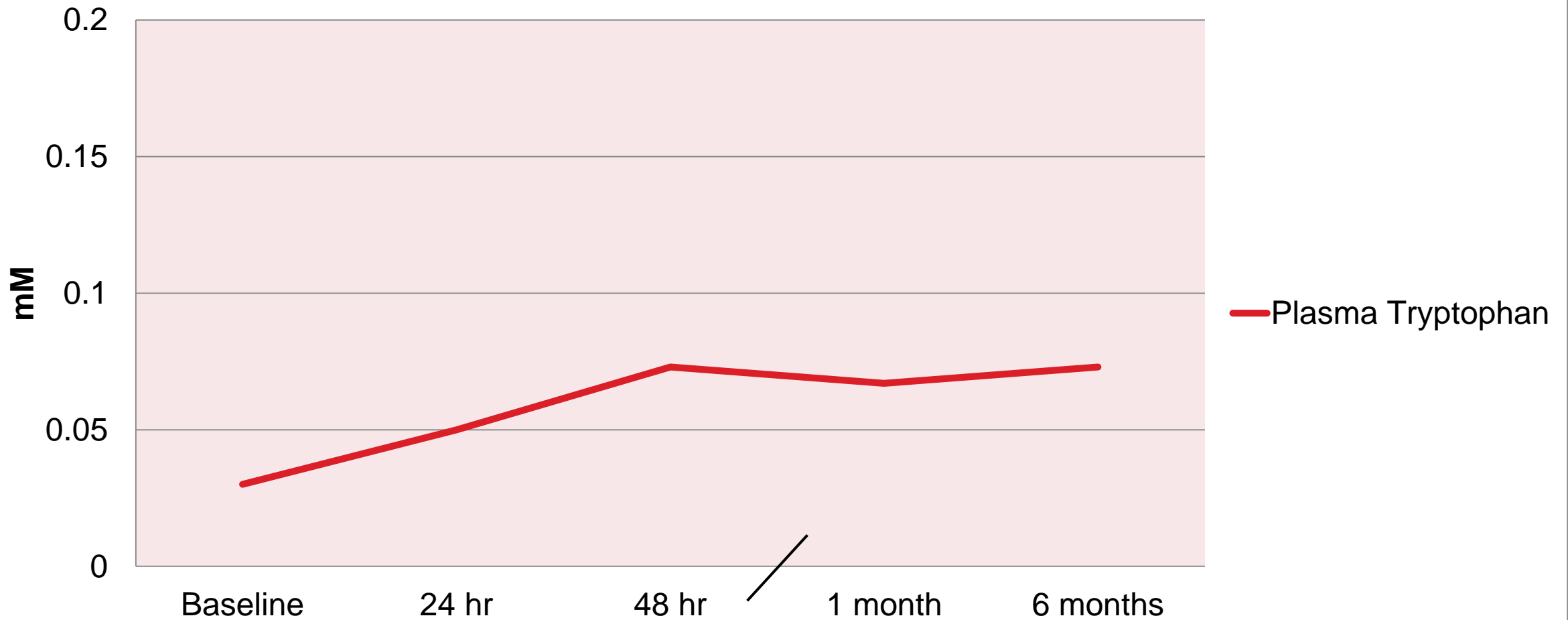
Brain Phe levels decreased over 6 months on LNAA

Mean Brain Phe Over 6 Months



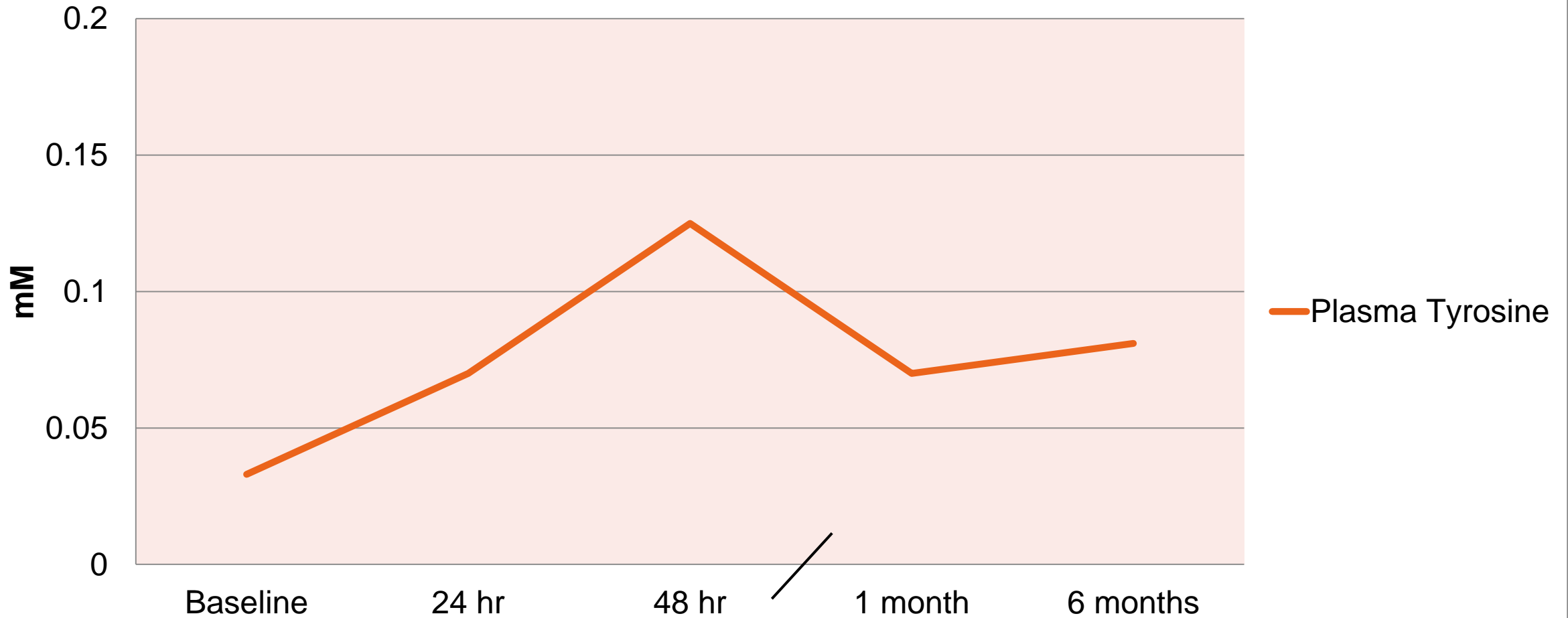
Plasma Trp levels increased over 6 months on LNAA

Mean Plasma Tryptophan Over 6 Months



Plasma Tyr levels increased over 6 months on LNAA

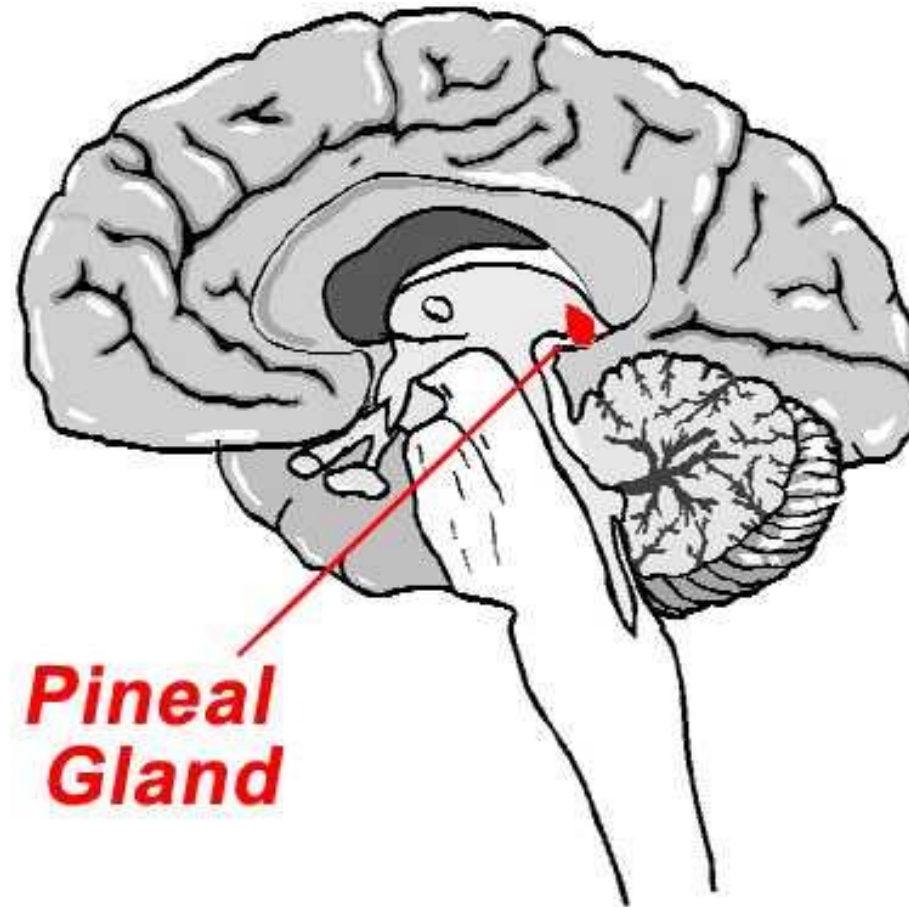
Mean Plasma Tyrosine Over 6 Months



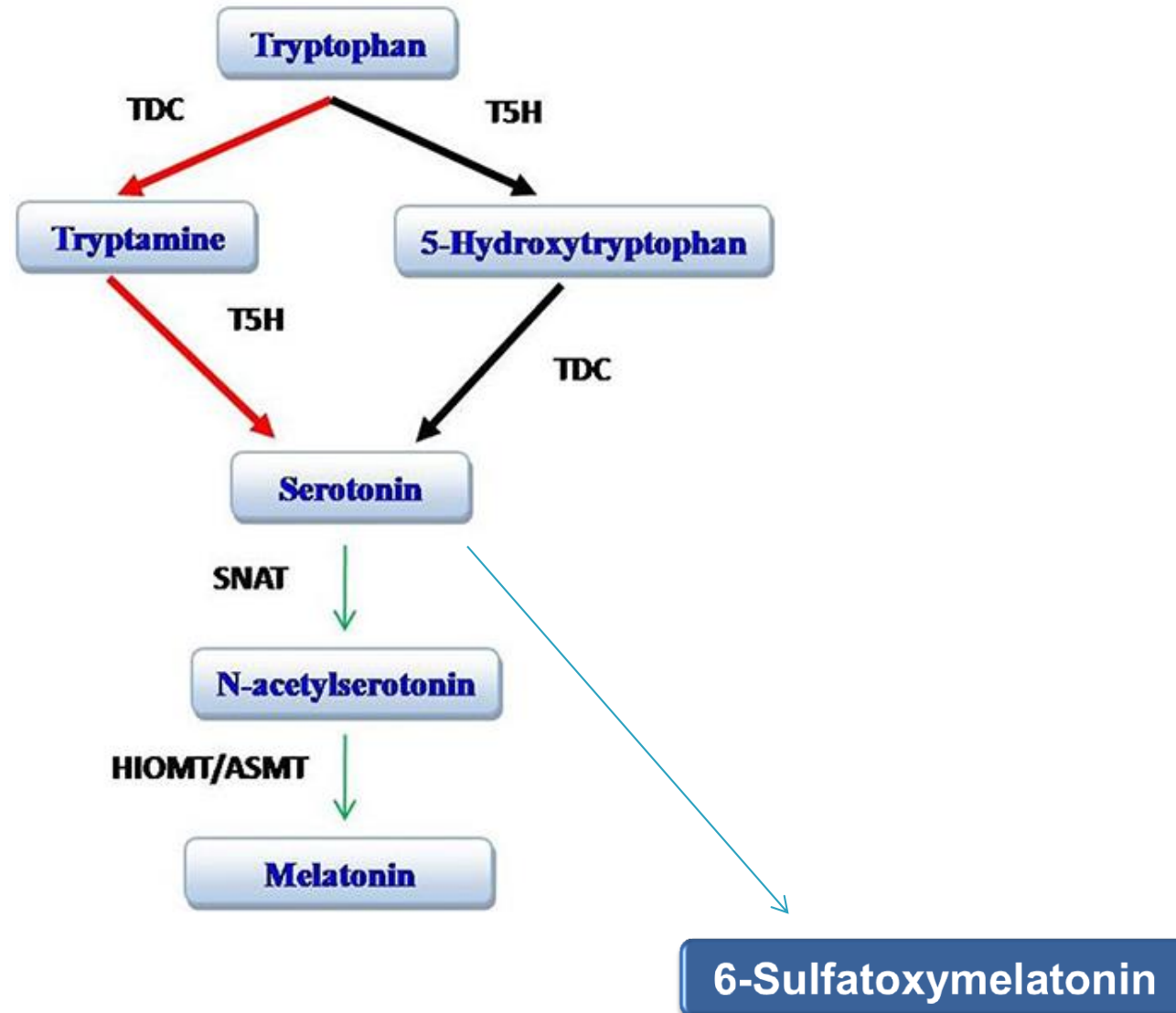
Could melatonin be a biomarker for effectiveness of LNAA?

- Yano S, et al. Large neutral amino acid supplementation increases melatonin synthesis in phenylketonuria: a new biomarker. *J Pediatr*. 2013 May;16(5):999-1003.
- Yano S, et al. Melatonin and dopamine as biomarkers to optimize treatment in phenylketonuria: effects of tryptophan and tyrosine supplementation. *J Pediatr*. 2014 Jul;165(1):184-189.
- Yano S, et al. Evaluation of tetrahydrobiopterin therapy with large neutral amino acid supplementation in phenylketonuria: effects on potential peripheral biomarkers, melatonin and dopamine, for brain monoamine neurotransmitters. *PLoS One*. 2016 Aug;11(8).

Pineal Gland-Third Eye



6-Sulfatoxymelatonin is a direct metabolite from Serotonin



Melatonin may be a biomarker for success of LNAA

- ❑ PKU Subjects showed low melatonin levels in blood and urine compared to controls
- ❑ LNAA supplementation increased nighttime blood melatonin levels, reflecting improved serotonin metabolism
- ❑ No further improvement shown with increased supplementation of Trp at 100mg/kg
- ❑ LNAA with BH4 supplementation showed further increase in serotonin metabolism with decrease of blood Phe-synergistic effects
- ❑ Monitoring urine melatonin may optimize and individualize management

How to calculate PKU diet with LNAA

- Total Protein = LNAA (20 or 30%) + Whole Protein (70 or 80%)
 - Use patient's ideal body weight (IBW)
 - Calculate protein requirements: 1g/kg IBW
 - Calculate 20-30% of protein needs for LNAA

- Maximum portion of PhenylAde[®] PheBLOC[™] is 45 tablets or 9 pouches per day



Example- 27 year old male 70kg

Tablets

- Protein = 1g/kg = 70g
- 20% from LNAA = 14g
- $14g \div 0.44 = 32$ tablets, 11 tablets tid with meals



1 tablet = 0.44g PE

OR quick calculation

- $70g \div 2 \div 3 = 11$ or 12 tabs tid
(not rocket science)



Example- 27 year old male 70kg

Powder

- Protein = 1g/kg = 70g
- 20% from LNAA = 14g
- $14g \div 2.2 = 6$ pouches/d (2 pouches tid with meals)



1 pouch = 2.2g PE

Implementing PhenylAde[®] PheBLOC[™] along with medical food

- 1) Start with **3-5 tablets or 1 pouch** per meal for a few days
- 2) **Gradually increase** to full dose by adding 3-5 tablets per meal or 1 pouch over the course of several days
- 3) Depending on whole protein intake, **consider reducing or increasing the amount of medical food**

Example

- Not taking medical food, not eating enough whole protein—implement medical food—protein shake!!
- Eating regular diet, does not need full portion of medical food, decrease medical food

Cautions when considering LNAA approach

- ❑ Over 12 years of age
- ❑ Not recommended with planning pregnancy or are pregnant
- ❑ Drug interactions
 - Always work with your patient's prescriber of SSRI's as LNAAs increases serotonin; same as SSRI's

Consideration when using LNAA approach

- Vitamin / Mineral supplementation
 - ▣ Fish oil
 - ▣ Vitamin B100 complex
 - ▣ Vitamin D



Monitoring parameters

- Nutrition assessment
 - ▣ Anthropometrics
 - ▣ Physical findings (eczema, etc)
 - ▣ Diet history

- Laboratory studies
 - ▣ Plasma amino acids
 - ▣ CBC, prealbumin, Vitamin D, homocysteine, essential fatty acids, comprehensive metabolic panel
 - ▣ Behavior assessment



Case Reports

Using LNAA in the dietary management of PKU



B, 17 year old male

- Wt: 95kg
- PhenylAde[®] PheBLOC[™] – 15 tabs once a day with a meal
- BH4 1400mg/d
- Medical foods provide: *(including PhenylAde PheBLOC)*
 - Protein: 57g
 - Tyr: 7785mg (82mg/kg)
 - Trp: 1818mg (19mg/kg)
- Averages approximately 25-30g whole protein/d
- Average blood Phe level ~12mg/dl

D, 16 year old male

- Wt: 63kg
- PhenylAde[®] PheBLOC[™] – 10 tabs tid with meals
- Medical foods provide: *(including PhenylAde PheBLOC)*
 - Protein: 73g
 - Tyr: 11,550mg (183mg/kg)
 - Trp: 3,060mg (49mg/kg)
- Averages approximately 25-30g whole protein/d
- Average blood Phe level ~15-20mg/dl

J, 50 year old male

- Wt: 80kg
- PhenylAde[®] PheBLOC[™] – 13 tabs tid with meals
 - Protein: 17g
 - Tyr: 7,800mg (95mg/kg)
 - Trp: 2,340mg (28mg/kg)
- Averages approximately 50g whole protein/d
- Average blood Phe level ~20-25mg/dl

LNAA successful in the late treated adult population

- Study of 14 late treated adults showing:
 - Behavior improvement
 - Less combative
 - Calmer
 - Increased communication abilities
 - Cost benefit analysis

Summary

- LNAA may be an alternative for adults and adolescents who cannot follow the Phe-restricted diet
- LNAA allows more whole protein
- LNAA can be used with other medical food products as well as BH4
- There is more to look at besides Phe- we need more biomarkers
 - Phe/Tyr ratio?? Urine 6-sulfatoxymelatonin?? Urine dopamine??

Questions—comments??



Stella Starlite

Feedback, Please!

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2. If not, please go to: <https://www.surveymonkey.com/r/LNAA>
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4. Go to www.NutriciaLearningCenter.com and enter the event code. Your certificate will be automatically downloaded to your NLC profile.

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