Survey of Palynziq®: An Enzyme Therapy that Modifies Phenylalanine (PHE) Metabolism in Patients Affected by Phenylketonuria (PKU)

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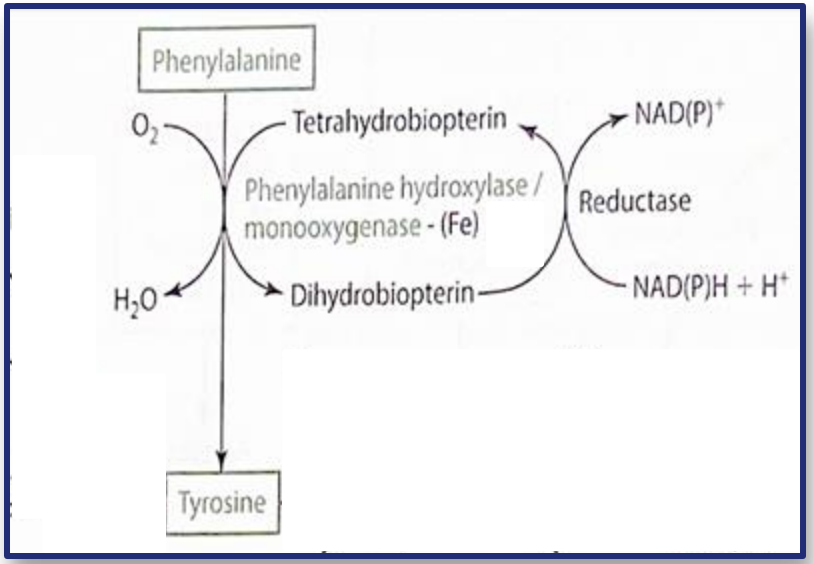
What is PKU?

- Phenylketonuria (PKU): inherited disorder of disrupted phenylalanine (PHE) metabolism
  - Build up of PHE in blood
  - Decreased tyrosine levels
- Results in two kinds of complications
  - Permanent neurological
    - Intellectual disabilities, paralysis
  - Functional/cognitive impairment
    - Seizures, psychiatric and attention problems, faulty reasoning, poor memory
- Newborn screenings and immediate initiation of PKU diet have decreased these phenotypes

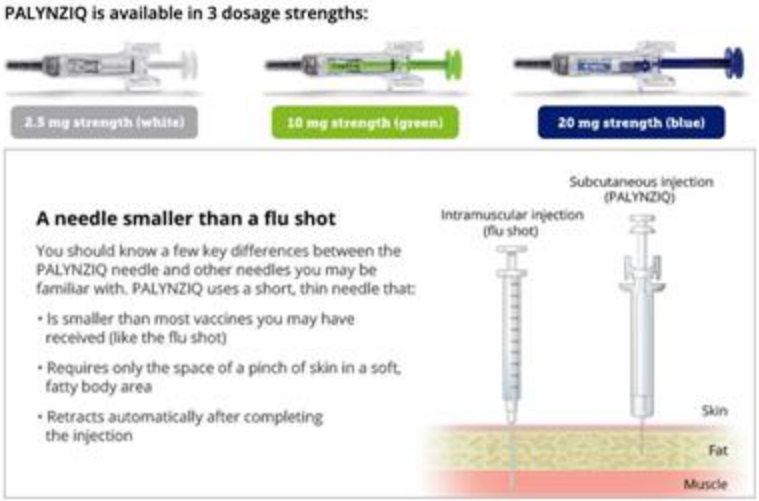
PHE Metabolism

- Digestion/Absorption/Transportation
  - PHE shares enzymes with other amino acids and aromatic amino acids
  - Serum PHE not impacted by these steps
- Metabolism/Catabolism
  - Enzyme: Phenylalanine hydroxylase (PAH)
    - Liver enzyme
    - Coenzyme: Iron, Vit C
    - Cosubstrate: BH_4 (tetrahydrobiopterin)
  - Product: Tyrosine
    - Conditionally essential



Palynziq®: What is it?

- Brand name of FDA approved drug (2018)
  - Pegvaliase-pqpz = Palynziq®
- Approved for adults, to treat hyper-phenylalanine
- Palynziq® = PEG + PAL !
  - Pegulated polyethylene glycol (PEG)
  - Phenylalanine ammonia lyase (PAL)
- Mechanism of action: PAL = plant enzyme
  - PAL reroutes PHE metabolism
  - Acts as substitute enzyme, replacing PAH
- Manufactured by BioMarin Pharmaceutical
- Injected subcutaneously, daily



Drug Treatment Process, Side Effects

- Treatment Process
  - Daily injections
  - Start: 5mg 2x per week
  - Typical titration dose: 20mg 1x day
  - Treatment for life
  - Additional Info: www.palynziq.com/starting-palynziq
- Side Effects - Immune Response
  - Rash, swelling at injection site
  - Hives
  - Joint pain
  - Anaphylactic shock*

Here is an example of how dosing with PALYNZIQ may look:

	Dose		Length of time[1]
Starting therapy	2.5 mg	once weekly	for at least 4 weeks
Increasing therapy	2.5 mg	twice weekly	for at least 1 week
	10 mg	once weekly	for at least 1 week
	10 mg	twice weekly	for at least 1 week
	10 mg	four times per week	for at least 1 week
	10 mg	once daily	for at least 1 week
Ongoing therapy[1]	20 mg	once daily	for at least 24 weeks
	40 mg	once daily	for at least 16 weeks
Maximum therapy[1]	60 mg	once daily	for up to 16 weeks

Child and Adult Doses (Auvi-Q®)

Thigh injection (EpiPen®)

** Must always carry Epinephrine autoinjector*

PHE Metabolism Before and After

Before Treatment

- PAH activity disrupted
- Little to no tyrosine made
- Excess serum PHE
  - Leads to excess phenylpyruvic acid

With Treatment

- Enzyme Substitution
  - PAL/Peg-PAL/Palynziq®
- Excess serum PHE metabolised:
  - Trans-cinnamic acid
  - Ammonia

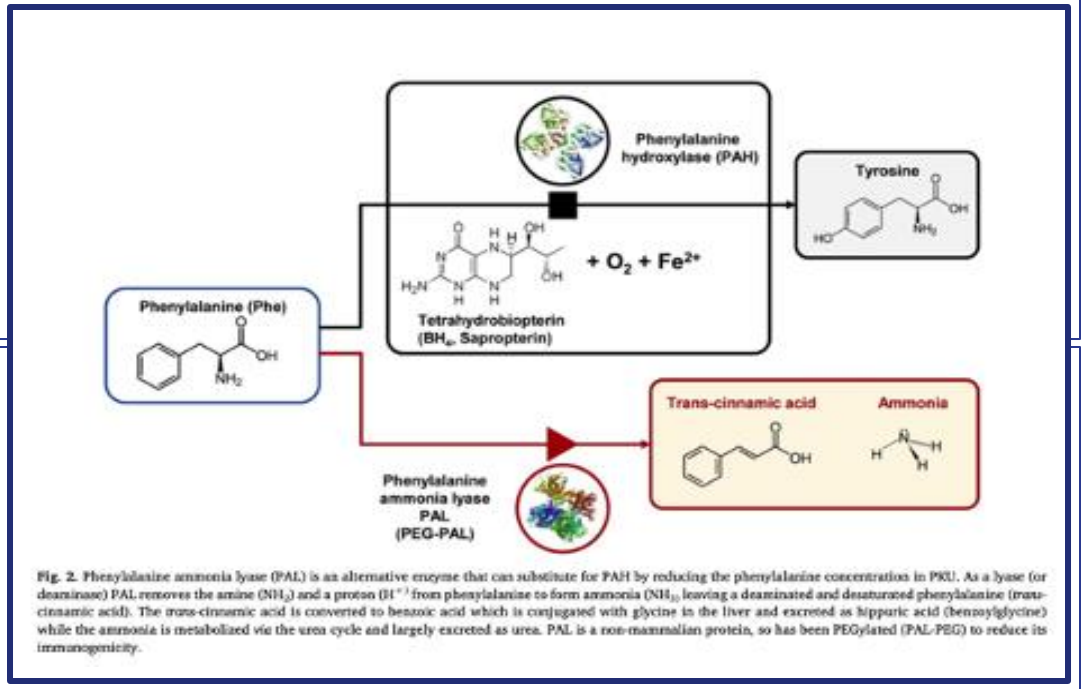


Fig. 2. Phenylalanine ammonia lyase (PAL) is an alternative enzyme that can substitute for PAH by reducing the phenylalanine concentration in PKU. As a lyase (or deaminase) PAL removes the amine (NH_2) and a proton (H^+) from phenylalanine to form ammonia (NH_3), leaving a deaminated and desaturated phenylalanine (*trans*-cinnamic acid). The *trans*-cinnamic acid is converted to benzoic acid which is conjugated with glycine in the liver and excreted as hippuric acid (benzoylglycine) while the ammonia is metabolized *via* the urea cycle and largely excreted as urea. PAL is a non-mammalian protein, so has been PEGylated (PAL-PEG) to reduce its immunogenicity.

PKU Diet Before and After

Before Treatment

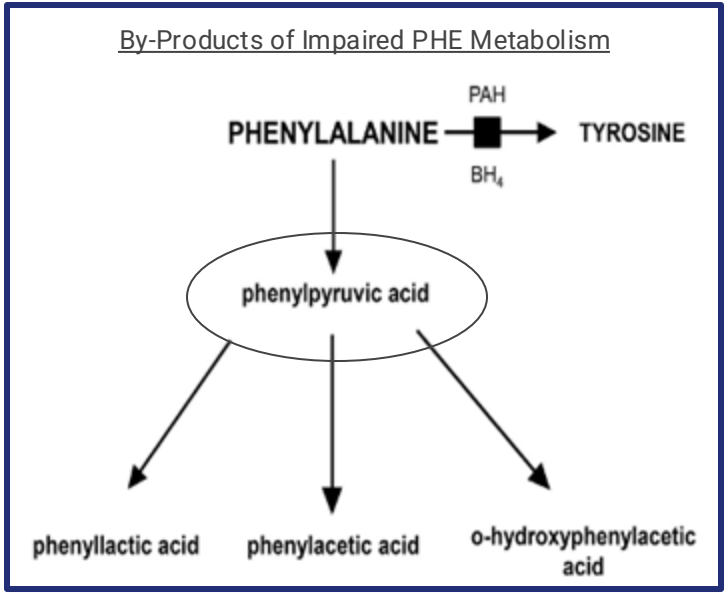
- Low PHE diet is crucial
- Primary diet: Medical food
  - PHE formula ensures adequate protein and essential nutrients are met
  - Fortified with tyrosine
- Avoid high protein foods:
  - Dairy, cheese, beans, peas, peanut butter, seeds, nuts, poultry, seafood, eggs, meat
- Foods to be consumed in moderation
  - Bread and crackers, snacks like popcorn and potato chips, fruits and vegetables (either whole or juiced), low-protein cereal, special low protein foods

After Treatment

- With Palynziq® no food off limits
- Same diet as those without PKU

Research Details - History of PAL: Plant Enzyme

- Long road to discovery: 1940's - 2018
- Research on plant metabolism for process of synthesizing lingin
  - Plants produce phenylpyruvic acid
    - Same metabolite made in humans with impaired PHE metabolism
  - Phenylpyruvic acid metabolized to cinnamic acid by PAL
- Toxicity studies conducted during WWII determined cinnamic acid was not harmful to humans in high doses
- Bacteria *Anabaena variabilis* is good source of PAL
- PAL manufacturing efforts developed
  - Increase enzymatic effect
  - Stabilize at room temperature



Research Details - Maternal PKU / Newborn Screening

- Expecting mothers with PKU
  - Should be attentive to PHE levels to prevent complications
    - Microcephaly, defects in heart and overall development
- Newborn screening for PKU
  - Blood test; Heel pricked to assess levels of PHE and tyrosine in blood
  - Ratio of PHE and tyrosine >3
- Other causes for high PHE levels
  - Liver dysfunction
  - BH_4 production/recycling disorder
  - Premature infants on parenteral nutrition
    - Amino acids part of solution

Blood Spot Test used for newborn screening and PHE monitoring

Research Details - Cofactors of Metabolism

- ~2,600 different PKU genotypes
- 1000+ variants of PAH activity
- Continuum of enzymatic activity
  - Severe (classic PKU): Null activity
  - Mild: Limited residual activity
- BH_4 deficiency = hyperphenylalaninemia
  - Similar effect as PKU, but distinct mechanism
    - Dihydropteridine reductase deficiency
    - Biopterin synthetase deficiency
  - Not strictly PKU
- PAL still beneficial for these forms of disorder

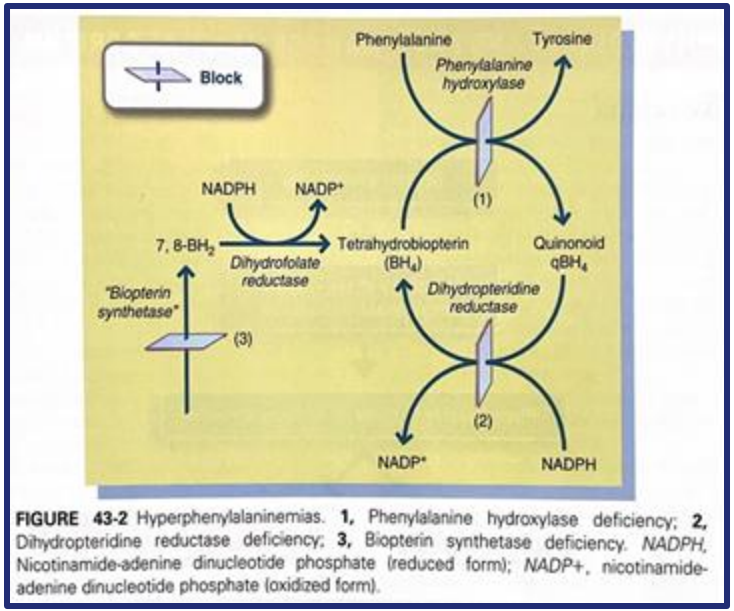
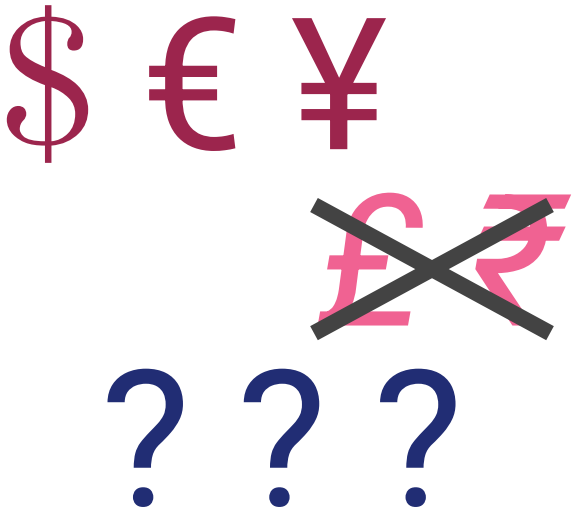


FIGURE 43-2 Hyperphenylalaninemias. **1,** Phenylalanine hydroxylase deficiency; **2,** Dihydropteridine reductase deficiency; **3,** Biopterin synthetase deficiency. *NADPH,* Nicotinamide-adenine dinucleotide phosphate (reduced form); *NADP+,* nicotinamide-adenine dinucleotide phosphate (oxidized form).

Limitations and Questions for Future Research

- Palynziq® not available worldwide
- Cost of treatment is expensive
- Newborn screening
  - Needs worldwide standardization
- Lack of research on if supplementation affects Palynziq® dosing
  - Lack of research for coenzyme vitamin C or iron supplementation to boost residual PAH activity in mild PKU cases uncertain of effects on drug dosing
  - Supplementation of cosubstrate BH_4 can enhance residual activity in some, mild PKU cases, uncertain of effects on drug dosing



Questions for Future Research, cont.

- In past, restricted diet treatment considered “cure” for PKU
  - Difficult to maintain
  - Evidence of negative impacts to executive function and mood, and measurable brain matter impacts, even with restricted diet
- Current research: recharacterize PKU as “brain” disease vs metabolic disorder
  - Long term studies needed to see if Palynziq® improves cognitive function
  - With Palynziq®: no blood-brain crossing of high PHE
    - No negative neuro-effects from diet fluctuations
  - Limited research on before and after cognitive effects of using Palynziq®
  - Preliminary research shows improvement in attention deficit, memory and mood
- Abstract submitted to National PKU Allied Disorders Association conference for research on before/after effects of Palynziq® treatment on neurocognitive function

Conclusion

- Palynziq® safe and effective with “miracle drug” effects on lifestyle
- Classic PKU
  - Diet from
    - 75% liquid diet (medical formula)
    - 3-5 grams of protein per day
  - Diet to
    - Unlimited protein - “liberalized” to eat anything
- Positive social impacts; able to eat “normal food”
- Manageable side effects
- Research still evolving in areas of neurocognition, maternal PKU, other uses of PAL enzyme, long term drug effects

Treatment offers diet liberalization and lifestyle normalization

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