Case 30
Phenylketonuria

Focus concept

The characteristics of phenylalanine hydroxylase, the enzyme missing in persons afflicted with the genetic disorder phenylketonuria (PKU), are examined.

Prerequisites

∙ Amino acid synthesis and degradation pathways.
∙ Integration of amino acid metabolic pathways with carbohydrate metabolic pathways.

Background

Phenylketonuria is an inherited disease which results from the lack of the enzyme phenylalanine hydroxylase (PAH). The PAH enzyme catalyzes the first step in the degradation of phenylalanine, as shown in Figure 30.1. In the phenylketonuric patient, phenylalanine accumulates which is eventually transaminated to phenylpyruvate, a phenylketone compound. Excess phenylpyruvate accumulates in the blood and urine and has the effect of causing mental retardation if untreated. Screening programs identify PKU babies at birth, and treatment consists of a low phenylalanine diet until maturation of the brain is completed. The structure and biochemical properties of the PAH enzyme have been well-studied.

The gene for PAH has been isolated and has been localized to chromosome 12. The PAH enzyme is a protein 451 amino acids in length with a molecular weight of 51,900 daltons. More than 60 different mutant genes giving rise to nonfunctional PAH proteins have been identified in PKU patients.

Questions

1. Is phenylalanine glucogenic, ketogenic, or both? Explain.

2. Next, kinetic studies were carried out with the enzymes. A plot of velocity vs. phenylalanine concentration yields a sigmoidally shaped curve. What does this tell you about the enzyme?

3. The effect of the hormones glucagon and insulin on PAH activity were investigated. The results are shown in Figure 30.4. In addition, the amount of radioactively-labeled phosphate incorporated into PAH with glucagon treatment was found to be nearly seven-fold greater than in controls.
   a. How would you interpret these data?
   b. Draw a diagram demonstrating the mechanism for hormonal activation of PAH.
   c. Which hormone activates PAH, and why?

4. Tyrosine is not an essential amino acid in normal persons, but it is essential in persons with PKU. Explain why.

5. Patients with the disease PKU tend to have blue eyes, fair hair, and very light skin. Explain why.
6. The cause for the mental retardation associated with untreated PKU is not completely understood, but it is believed to arise from the high concentrations of phenylpyruvate, which is a product of a transamination reaction with phenylalanine and α-ketoglutarate. The phenylpyruvate is believed to be toxic to the developing brain. Write the balanced equation for the transamination of phenylalanine to phenylpyruvate, and include the structures of the reactants and products. Identify any cofactors needed to accomplish the reaction.

7. The mental retardation associated with phenylalanine can be avoided if the neonate is immediately placed on a low phenylalanine diet for the early years, and perhaps for life.
   a. Why is a PKU patient placed on a low phenylalanine diet instead of a phenylalanine free diet?
   b. The artificial sweetener Nutrasweet ® contains the compound aspartame, which consists of a methylated Asp-Phe dipeptide. (The C-terminal carboxyl group is methylated.) Draw the structure of aspartame. If you were a physician, what advice would you give to a PKU patient regarding this product? If you were a manufacturer of aspartame, what would your responsibility to your customers be?

**Figure 30.4:** Percent activity (as compared to control) of PAH in the presence and absence of insulin, glucagon, and/or preincubation with phenylalanine.
Figure 30.1. Phenylalanine and tyrosine metabolism. BH$_4$ is tetrahydrobiopterin, an essential cofactor for phenylalanine hydroxylase

References