Phenylalanine Metabolism: Phenylketonuria

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Phenylketonuria is most commonly caused by a deficiency of phenylalanine hydroxylase, which converts phenylalanine into tyrosine

Phenylketonuria (PKU) is one of the most common aminoacidurias, with an occurrence of 1 in 20,000 live births. In addition to “classical” PKU (Fig. 44-4, reaction 1), many youngsters have hyperphenylalaninemia caused by a partial deficiency of the enzyme. They do not suffer mental retardation, but they may have more subtle neurological problems.

The hydroxylase is a trimer of approximately 150 kDa of identical subunits and is located predominantly in the liver. The enzyme has been mapped to human chromosome 12q22-24.1, where the gene comprises 13 exons extending over 90 kb of genomic DNA. Deletions in the gene are not common. A frequent cause among northern Europeans (~40%) is a G-to-A transition at the 5′ donor splice site in intron 12, resulting in absence of the C-terminus. Another relatively common (~20%) mutation in northern Europeans involves a C-to-T transition in exon 12, resulting in substitution of a tryptophan for an arginine residue. Over 70 different mutations have been described to date in the American population.

Mutations have been associated with specific haplotypes, the latter determined by analysis of restriction fragment length polymorphisms. This approach has been utilized for prenatal diagnosis. The study of haplotypes also has revealed that the majority (~75%) of northern European patients are compound PKU heterozygotes.

Affected babies are not retarded at birth, but almost all will be impaired if they are not treated by 3 months of age. Mass screening has largely eliminated the untreated PKU phenotype of eczema, poor growth, irritability, musty odor caused by phenylacetic acid and tendency to self-mutilation.
Progressive motor dysfunction has been described in children with long-term hyperphenylalaninemia.

The clinical utility of dietary restriction of phenylalanine to 200 to 500 mg per day is clear. Well-controlled patients have normal intelligence, although there is an increased risk of perceptual learning disabilities, emotional problems and subtle motor difficulties. Diet therapy is maintained throughout adolescence and, perhaps, indefinitely. Performance may deteriorate after the diet is discontinued.

Exposure to excessive (>1 mM) blood phenylalanine concentrations in early infancy can impair neuronal maturation and the synthesis of myelin. The responsible factor is excess phenylalanine, not a phenylalanine metabolite or tyrosine deficiency. One hypothesis suggests that excessive phenylalanine inhibits the transport of other neutral amino acids across the blood—brain barrier. Conversely, some have proposed that high intracerebral phenylalanine concentrations impair the transport of tyrosine from the brain to the blood. High brain phenylalanine concentrations can inhibit synaptosomal Na,K-ATPase activity and the synthesis of neurotransmitters. Excess phenylalanine also causes disaggregation of brain polysomes, which may explain the dysmyelination that has been described in the phenylketonuric brain. A loss of neurotransmitter receptors has been described in a murine model of hyperphenylalaninemia.

The genotypically normal offspring of an untreated mother may have microcephaly and irreversible brain injury, as well as cardiac defects. Scrupulous monitoring of dietary phenylalanine intake in these women has resulted in a much better outcome.

Phenylketonuria may also be caused by defects of biopterin metabolism

The electron donor for the phenylalanine hydroxylase is tetrahydrobiopterin (BH$_4$), which transfers electrons to molecular oxygen to form tyrosine and dihydrobiopterin (QH$_2$) (Fig. 44-4, reaction 2). BH$_4$ is regenerated from QH$_2$ in an NADH-dependent reaction (Fig. 44-4, reaction 2) that is catalyzed by dihydroypteridine reductase (DHPR), which is widely distributed. In the brain, this enzyme also mediates hydroxylation of tyrosine and tryptophan.
Human DHPR has been mapped to chromosome 4p15.1-p16.1. The coding sequence shows little homology to other reductases, for example, dihydrofolate reductase.

In rare instances, PKU is caused by defects in the metabolism of BH₄, which is synthesized from GTP via sepiapterin (Fig. 44-4, reactions 3 and 4). BH₄ functions also in the hydroxylation of tyrosine and tryptophan.

Even careful phenylalanine restriction fails to avert progressive neurological deterioration because patients are unable to hydroxylate tyrosine or tryptophan, the synthesis of which also requires BH₄. Thus, neurotransmitters are not produced in sufficient amount.

Patients sustain convulsions and neurological deterioration. The urine contains low concentrations of the metabolites of serotonin, norepinephrine and dopamine. The reductase also plays a role in the maintenance of tetrahydrofolate concentrations in brain, and some patients have had low folate in the serum and CNS. Treatment has been attempted with tryptophan and carbidopa to improve serotonin homeostasis and with folinic acid to replete diminished stores of reduced folic acid. This therapy sometimes is effective. Diagnosis involves assay of DHPR in skin fibroblasts or amniotic cells. Phenylalanine hydroxylase activity is normal.

Other causes of PKU secondary to defective BH₄ synthesis include GTP cyclohydrolase deficiency and 6-pyruvoyltetrahydrobiopterin synthase deficiency. Patients with either defect have psychomotor retardation, truncal hypotonia with limb hypertonia, seizures and a tendency to hyperthermia. Intravenous administration of BH₄ may lower blood phenylalanine concentrations, but this cofactor may not readily cross the blood—brain barrier. Treatment with synthetic pterin analogs or supplementation with tryptophan and carbidopa may prove more efficacious, particularly if treatment is started early in life.

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The phenylalanine hydroxylase (PAH) pathway. Phenylketonuria usually is caused by a congenital deficiency of PAH (reaction 1), but it also can result from defects in the metabolism of biopterin, which is a cofactor for the hydroxylase. Enzymes: 1, phenylalanine hydroxylase; 2, dihydropteridine reductase; 3, GTP cyclohydrolase; 4, 6-pyruvoyltetrahydrobiopterin synthase. QH₂, dihydrobiopterin; BH₄, tetrahydrobiopterin; DEDT, d-erythro-dihydronopterin triphosphate.