

PKU OR HOW TO KEEP YOUNG BRAINS HEALTHY

Children with phenylketonuria, commonly known as PKU, lack the ability to break down the amino acid phenylalanine. They must avoid eating the many foods containing this substance because over time it will build up in their bodies, affecting their nervous system and potentially leading to severe mental retardation.

Phenylalanine is a building block of protein, and it's in all types of animal products, including meat and dairy. It's also present in wheat. Imagine growing up without ever tasting regular pizza, hamburgers, hot dogs, bread or ice cream. To make matters worse, those with PKU also have to drink a special, not particularly palatable, formula to make sure they receive the nutrients they need.

While young children whose diets are largely controlled by their parents usually stick to safe foods, adolescents with PKU often have a more difficult time. Going off their diet does not make them immediately ill, but it can have a long-term effect on their neurological development, causing problems such as lowered intelligence.

No cure for PKU is available yet, but a international team led by Dr. Harvey Levy at Children's Hospital Boston and involving Canadian researcher Dr. Annette S. Feigenbaum at the Hospital for Sick Children in Toronto, may have found a way to help. They tested a compound known as tetrahydrobiopterin, or BH4, in nearly 90 young people with PKU to see whether taking it could reduce the blood concentration of phenylalanine. BH4 works by boosting the effects of any residual amounts of phenylalanine hydroxylase—the enzyme that breaks down phenylalanine—that might be present in the bodies of those with PKU.

After 6 weeks, the BH4 did work, but only partially and only in some patients. Levy estimates that about 40% of those with PKU have some sort of response to BH4 but only about 25% have a meaningful response. *"Some patients can go off the diet completely, but those are unusual,"* he says. *"The majority of patients who respond will be able to increase the amount of protein they can*



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take in their diet and may or may not be able to decrease the amount of formula."

While this study was conducted primarily in adolescents, what's particularly exciting is the role BH4 might play in younger children—the effects of the buildup of phenylalanine in those with PKU is cumulative, so the sooner it can be halted, the less likely patients are to suffer from long-term neurological and cognitive deficits. Levy says they have already begun testing BH4 in children under the age of 4.

Dr. Grant Mitchell, a PKU expert at CHU Sainte-Justine points out that we've come a long way in the management of PKU. *"Until the mid-20th century,"* he says, *"patients with PKU were common in institutions for the mentally retarded. PKU was the first example of mental re-*

tardation with a known chemical cause. Since the 1960s, neonatal PKU screening has been adopted in all developed countries, permitting early diagnosis and treatment. The outcome of PKU has improved immeasurably, and two generations of neonatally-screened, treated patients have normal intelligence."

These findings, Mitchell says, move PKU treatment forward. *"This article represents a new step from the clinical laboratory towards a normal life for PKU patients but this journey is not ended. The study is also a reminder that biochemical genetic conditions are important considerations in the treatment and prevention of mental retardation."* 🦋

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Ref.: Levy HL, Milanowski A, Chakrapani A, Cleary M, Lee B, Trefz FK, Whitley CH, Feillet F, Feigenbaum AS, Bedchuk JD, Christ-Schmidt H, Dorenbaum A, Sapropterin Research Group. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6r-Bh4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase Iii randomized placebo-controlled study. *Lancet* 2007;370(9586):504-510.