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Is Melatonin Synthesis a New Biomarker for the Pathogenesis and Treatment of Phenylketonuria?

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More than 30 years ago, Charles Scriver and Carol Clow described phenylketonuria (PKU) as the epitome of biochemical genetics, the disorder from which much of our model for diagnosing, treating, and understanding inborn errors has derived.¹ They placed PKU at this pinnacle because it was the disorder among the inborn errors in which the clinical biochemistry, the clinical effects, the enzymatic deficiency, the involvement of an endogenously synthesized cofactor, its genetic heterogeneity, and a number of other features had been described.

At that time the only treatment was dietary, but now newer treatments, such as large neutral amino acids (LNAAs) and the enzyme cofactor tetrahydrobiopterin (Kuvan; Biomarin, Novato, California), have been developed and marketed.² These therapies have introduced the hope of easier treatments with enhanced compliance and improved outcome but have still to prove their long-term benefits. What has eluded us in PKU, as it has in all other inborn errors of metabolism, is a clear definition of its pathogenesis and thus clear points at which successful intervention, other than lowering plasma phenylalanine levels, might occur.

Some years ago, a Danish group showed that those with untreated PKU and high blood phenylalanine levels associated with low cerebrospinal fluid levels of tyrosine and tryptophan and inferred from additional cerebrospinal fluid measurements that the levels of their metabolites—the neurotransmitters L-dopa (the dopamine precursor) and 5-OH tryptophan (the serotonin precursor), respectively—were also reduced.³ They hypothesized that these abnormalities play a role in the pathogenesis of the brain damage in PKU. What has been lacking in this biochemical and neurophysiologic “snapshot” is a way, other than via unacceptably intrusive repeated lumbar punctures, to assess brain metabolites and their effects in a repeated and reproducible manner. Thus, measuring the biochemical efficacy of our treatment of PKU by repeated sampling of blood and urine has the advantage of

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practicality. Plasma phenylalanine levels are the benchmark of effective therapy and have correlated with the spectacular success of PKU treatment since newborn screening made early treatment universal >40 years ago. The phenylalanine levels alone, however, do not explain the imperfection of this correlation or the mechanism for pathogenesis of the brain toxicity. What is needed has been a biochemical marker that can provide a better index of the impact of elevated phenylalanine and perhaps a finer marker of the efficacy of our therapies.

In this issue of *The Journal*, Yano et al has suggested an alternative biomarker that might provide insight into the brain toxicity of PKU.⁴ That melatonin is synthesized only in the pineal gland of the hypothalamus exclusively from serotonin has been known for a number of years, as has the fact that its only excretory metabolite is sulfatoxymelatonin.⁵ Yano et al recognized that this unique metabolic pathway may be useful as a surrogate marker for the efficacy of the diet and more remotely as a pathogenic marker of a process known to occur only in brain. These studies tested the effect of supplementation of nonphenylalanine LNAAs on melatonin synthesis as a treatment for PKU. In a double-blinded crossover study, the patients were given either a protein-controlled meal alone or this meal plus an LNA supplement. The patients who received the meal alone had markedly elevated plasma phenylalanine levels and significantly reduced ratios of both tyrosine and tryptophan levels to the other LNAAs (including phenylalanine), as well as significantly reduced levels of plasma melatonin and urine sulfatoxymelatonin. When given LNAAs, which are thought to increase the levels of tyrosine and tryptophan in the brain, the level of plasma tryptophan and the levels of both plasma melatonin and urinary sulfatoxymelatonin improved in a statistically significant manner. The tyrosine level also rose with an increase in urinary dopamine, its metabolite, but the significance of this finding is muted by the fact that it is produced in the periphery and cannot be used to infer specificity of central nervous system dynamics. Although the response of these metabolites to treatment with LNAAs may imply efficacy of this treatment, the effect was relatively limited and the changes or improvements, although statistically meaningful, did not approach normal levels. However, the possibility of defining a peripheral marker that implies central nervous system benefit of therapy as well as brain toxicity is exciting.

These findings require validation. Can they be reproduced in a larger PKU population, and will reduced melatonin synthesis be a true and linear reflection of the danger of elevated phenylalanine levels? Will these findings be corroborated at the tissue level in the mouse model for PKU? Will in vitro studies further corroborate the findings at a tissue and cellular level? Most importantly, will these findings lead to alteration in the way PKU is followed or treated? If the answer to these questions is in the affirmative, Yano et al will have provided us with a new way to study PKU and its treatments.

This work is admirable in its simplicity and directness. It required no substantial funding, no new techniques, and no expensive molecular studies. Instead, it required insight and ingenuity—hallmarks of science. Whether it is a lasting advance or a “shooting star whose glow rapidly fades,” it does indicate that the age of originality and imagination is not dead.

Glossary

LNAA	Large neutral amino acid
PKU	Phenylketonuria

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