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Tetrahydrobiopterin-responsive hyperphenylalaninaemia due to homozygous mutations in the phenylalanine hydroxylase gene

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Sir: Steinfeld et al. [3] reported on three infants with tetrahydrobiopterin (BH₄)-responsive phenylalanine hydroxylase (PAH) deficiency, one of them with a common homozygous Y414C mutation. They questioned the concept of decreased cofactor affinity as a valid explanation for BH₄ responsiveness. Recently, we published the first patient with a homozygous L48S mutation presenting with a BH₄-responsive PAH deficiency [1]. While some of mutations in the *PAH* gene may produce Km variants which can be activated by BH₄ (I65T, V190A, A241C, R261Q, A313T, A373T, E390G, A395P, A403V, P407S, Y414C) the L48S mutation is not located in the DNA coding region for the catalytic domain. Previously described patients were all compound heterozygotes for the above listed mutations and most of these mutations proteins showed 20%–30% residual activity when recombinantly expressed in eukaryotic cell systems[1]. Thus, mechanisms different from the low cofactor affinity may be responsible for the phenotype in patient with the L48S mutation.

The recent finding that BH₄ (200 mg/kg ip) increases the PAH mRNA, enzyme activity and protein levels by 50% in a *hph-1* mouse suggested the BH₄ can regulate *PAH* gene expression [2]. We proposed that in patient with the L48S mutation, and this may also be true for some other homozygous mutations, BH₄ increases

enzyme activity by inducing the gene expression. However, one cannot exclude that in some patients the BH₄ responsiveness is due to both a Km variant and increased *PAH* gene expression.

These data stress the importance of the BH₄ loading test and of BH₄ as a potential practical alternative in the treatment of mild hyperphenylalaninaemia. Our preliminary data indicate that BH₄-responsive PAH deficiency is more common than initially assumed. Around 70% of patients with initial plasma phenylalanine levels below 800 µmol/l respond to the loading test with 20 mg BH₄/kg body weight (C. Bernegger and N. Blau, unpublished observation).

References

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