Dihydropteridine Reductase and Folate Metabolism Revisited

Robert J Leeming, S Kate Hall

Screening Laboratory, Clinical Chemistry Department, Childrens Hospital Birmingham, West Midlands, B4 6NH, United Kingdom

Date received: 2010/08/07

To the Editor:

Whilst the role of dihydropteridine reductase (DHPR) in folate metabolism has never been proven experimentally, there is little clear evidence in the literature that dihydrofolate reductase (DHFR) is present in human brain. In the absence of DHFR in the brain then DHPR is almost certain to have a crucial role in maintaining reduced folate concentrations and this has been suggested previously (1). Further, as the folate concentration in the cerebrospinal fluid (CSF) is approximately double that in blood plasma, this indicates active rather than passive transport across the blood brain barrier. In patients with untreated DHPR deficiency, folate deficiency develops. Although there have been some reports of folate deficiency in the periphery, it is extreme in the central nervous system (CNS). The good response of DHFR deficient patients to folate therapy in the form of 5-formyltetrahydrofolic acid, folinic acid, a compound not found in nature has long been known (2). Following FA administration, the already low concentrations of 5-methyltetrahydrofolic acid in the CSF in the DHPR deficient patient fall to catastrophically low levels and marked physical changes in the brain develop (3). One explanation has been that the folate deficit in this disorder is caused by the accumulation of 7,8-dihydrobipterin, 7,8-BH2, as 7,8-BH2 is also a substrate for dihydrofolate reductase (DHFR) in addition to 7,8-dihydrofolate. 7,8-BH2 accumulation thereby could interfere with folate metabolism. However, there are many other situations where 7,8-BH2 is increased markedly without obvious clinical effect. Classical phenylketonuria is one of such cases (4) and there are several iatrogenic causes. Another explanation has been the effect of quinonoid dihydrobipterin (q-BH2), on 5,10-methylenetetrahydrofolate reductase, although q-BH2 is very unstable. Neither of these postulates explains the specific lowering of CNS 5-methyltetrahydrofolic acid, although other gross changes in folate metabolism occur in classical phenylketonuria (5)

Folate in unfortified food is either in the tetrahydro or dihydro form. The model we are proposing is that, whilst folate is normally maintained, in the periphery, in its metabolically active reduced state largely by DHFR, in brain it is taken up and concentrated in the CSF and in contrast maintained by DHPR. When (synthetic) FA is administered, it passes through the gut wall unaltered, is reduced first to 7,8-dihydrofolic acid and then to tetrahydrofolic acid in the liver by DHFR (6). The first of these reductions is slow and a significant proportion of unmetabolised FA passes through to the bloodstream (7). We hypothesise that FA then competes with the transport of the major form of folate in the body, 5-methyltetrahydrofolic acid, through the blood brain barrier.

In summary, in DHPR deficiency, the brain is reliant on 5-methyltetrahydrofolic acid passing the blood brain barrier and as this cannot be recycled to a reduced state in the absence of both DHFR and DHPR activity, CSF folates fall. When FA is administered then replenishment of this limited supply to the brain is blocked and the consequence is catastrophic. Our observations given here, taken individually, are not entirely novel but when put together, in addition to providing a plausible explanation for folate deficiency in DHPR deficiency, they add weight to the role of DHPR in folate metabolism, which may have significance in the periphery as well as being crucial in the CNS. We have previously suggested (8) that further proof might be found in the extremely rare 4a-carbinolaminolatedehydratase deficiency if 7-substituted folates were to be demonstrated in the CSF or even, in blood and urine.
References