Journal of Neurology, Neurosurgery, and Psychiatry 1987;**50**:242–243

Matters Arising

Biopterins in arginase, dihydropteridine reductase and phenylalanine hydroxylase deficiency

Sir: We have reported a child with arginase deficiency who had a disturbance of central monoamine metabolism which resembled that seen in patients with phenylalanine hydroxylase (PH) deficiency.[1] Cutler[2] suggests that in both disorders the amine changes might be secondary to a decreased activity of dihydropteridine reductase (DHPR). Inherited deficiency of this enzyme, which recycles tetrahydrobiopterin, the cofactor for the aromatic amino acid hydroxylases, leads to defective amine synthesis[3] and in addition' to an increase in the concentrations of total biopterins in urine,[4] CSF,[5] and blood,[6] due mainly to accumulation of dihydrobiopterin.

If Cutler's proposal was correct one might expect a similar increase in biopterins to occur in patients with arginase or phenylalanine hydroxylase deficiencies when the plasma arginine or phenylalanine concentrations were raised. Patients with PH deficiency do show a rise in biopterins which is proportional to the rise in phenylalanine. We have demonstrated, however, that the rise in the CSF is due to tetrahydrobiopterin in PH deficiency and dihydrobiopterin in DHPR deficiency,[7] indicating that the mechanism for the rise is likely to be different in the two disorders.

At the time of investigation of the patient with arginase deficiency, methods were not available for measurement of the individual biopterin species in CSF. CSF total biopterins were, however, measured using *Crithidia* assay[8] (3·8 and 2·1 ng/ml, control mean 3·7 ng/ml s.d. ± 0·8) and using HPLC following manganese dioxide oxidation[9] (6·0 and 5·4 ng/ml, control mean 4·78 s.d. ± 1·75). These normal values contrast with the increase in biopterins in CSF found using the *Crithidia* assay in four patients with PH deficiency (range 5·4–16 ng/ml) and one patient with DHPR deficiency (range 9–11 ng/ml), and similarly using the HPLC assay in one patient with PH deficiency (19·1 ng/ml) and two patients with DHPR deficiency (range 9·1–18·9 ng/ml).

Whole blood total biopterins (4·8–6·0 ng/ml) and DHPR activity (135–141 umol/min/l) were also normal in the patient with arginase deficiency and did not alter when the hyperargininaemia was corrected. In PH deficiency, whole blood DHPR activity is also unaffected.[10] Indeed whole blood DHPR activity is used to distinguish between deficiency of this enzyme and PH.[10]

These results do not support the idea that arginine and phenylalanine inhibit DHPR activity in subjects with arginase or PH deficiency.

KEITH HYLAND
ISABEL SMITH
JAMES V LEONARD
Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK.

References

1 Hyland K, Smith I, Clayton PT, Leonard JV. Impaired neurotransmitter amine metabolism in arginase deficiency. *J Neurol Neurosurg Psychiatry* 1985;**48**:1188.
2 Cutler P. Arginase deficiency and phenylketonuria. *J Neurol Neurosurg Psychiatry* 1986;**49**:1090.
3 Butler IJ, Krumholz A, Holtzman NA, Koslow SH, Kaufman S, Milstein S. Dihydropteridine reductase deficiency variant of phenylketonuria: a disorder of neurotransmitters. *Trans Am Neurol Assoc* 1975; **100**:5.
4 Milstein S, Kaufman S, Summer GK. Hyperphenylalaninaemia due to dihydropteridine reductase deficiency: diagnosis by measurement of oxidised and reduced pterins in urine. *Pediatrics* 1980;**4**:806–10.
5 Smith I, Hyland K, Kendall B, Leeming R. Clinical role of pteridine therapy in tetrahydrobiopterin deficiency. *J Inher Metab Dis* 1985;**8:Suppl.1**:39–45.
6 Rey F, Harpey R, Leeming RJ, Blair JA, Aicardi J, Rey J. Les hyperphenyalaninemies avec activité normal de la phenylalanine-hydroxylase—le deficit en tetrahydrobiopterin et le deficit en dihydropteridine reductase. *Arch Fr Pediatr* 1977; **34**:109–20.
7 Howells DW, Smith I, Hyland K. Estimation of tetrahydrobiopterin and other pterins in cerebrospinal fluid using reverse-phase high-performance liquid chromatography with electrochemical and fluorescence detection. *J Chromatogr* 1986;**381(2)**:285–94.
8 Smith I, Leeming RJ, Cavanagh NCP, Hyland K. Neurological aspects of biopterin metabolism. *Arch Dis Child* 1986;**61**:130–7.
9 Hyland K, Smith I, Howells DW, Clayton PT, Leonard JV. The determination of pterins, biogenic amine metabolites and aromatic amino acids in cerebrospinal fluid using isocratic reverse phase liquid chromatography with in series dual cell coulometric electrochemical and fluorescence detection: Use in the study of inborn errors of dihydropteridine reductase and 5,10-methylene-tetrahydrofolate reductase. In: Wachter H, Curtius H-Ch, Pfleiderer W, eds. *Biochemical and Clinical Aspects of Pteridines. Vol 4.* 1985:85–99.
10 Leeming RJ, Barford PA, Blair JA, Smith I. Blood spots on Guthrie cards can be used for inherited tetrahydrobiopterin deficiency screening in hyperphenylalaninaemic infants. *Arch Dis Child* 1984;**59**:58–61.

The dementia of Alzheimer's disease: an update

Sir: Neary and colleagues[1] argue that the dementia of Alzheimer's disease (AD) is largely a reflection of the degeneration of pyramidal, non-cholinergic, cortical neurons. An experiment we have carried out in the rat suggests a mechanism whereby degeneration of glutamic and aspartic (dicarboxylic) acid-releasing, non-cortical, neurons causes this dementia.

An electrolytic lesion was placed in the left amygdala of six 37 day old male Wistar rats from an inbred in-house colony under ether anaesthesia. The lesion was made stereotaxically at two sites (in the central part of the anterior half of the amygdala and the second in the posterior half) using an insulated electrode (5 μA passed for 1 min at each site). Animals were killed 54/55 days after surgery. The electrode track in all cases passed through the dorsolateral cerebral cortex and the lateral margin of the striatum, to the amygdala. In no animal was there any evidence of damage along the track other than that small amount attributable to the passage of the electrode. The left amygdala had been completely destroyed in all animals by the lesion, with slight involvement of the adjacent pyriform cortex but with no damage of other structures recognised and no involvement directly of the substantia innominata or basal nucleus itself. The entire extent of the nucleus basalis of Meynert (nbM) was dissected[2] and, along with tissue from six unoperated animals, was homogenised in 10 mM Tris-HCl, pH 7·4, containing 0·32 M sucrose and 1 mM EDTA using a glass-teflon homogeniser. (The 12 animals came from two litters, six in each, three from each litter being operated on). High affinity Na^+-dependent uptake of D-[^{3}H]-aspartic acid was assayed[3] using 300 nM of substrate and a Krebs Ringer phosphate buffer containing either 161 mM Na^+ (A) or 20 mM Na^+ and 141 mM choline chloride (B). The Na^+-dependent uptake value (A minus B, pmoles/mg protein/min ± SD) of the left nbM from the lesioned animals was 28·2 ± 12·0 units. The control Na^+-dependent uptake values were 63·5 ± 21·7 units (right