Brain MRSI Metabolic Study of Patients with Remethylation Deficiency

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INTRODUCTION

Genetic deficiencies impairing the intracellular metabolism of the vitamin B12 (cobalamin (Cbl) deficiency) and folic acid (caused by a 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency) cause remethylation deficiency (RD) metabolic diseases characterized by homocystinuria and a low concentration of methionine which severely affect the central nervous system (1). Based on early work on humans on special diets (2), the main contribution to homocysteine (Hcy) synthesis has been attributed to the conversion of guanidinoacetic acid (GAA) to creatine (Cr) by guanidinoacetate methyltransferase (GAMT) (see Fig. 1). However, the predominant contribution of Cr as methyl acceptor has been challenged recently on the basis of studies performed on phosphatidylethanolamine *N*-methyltransferase (PEMT) knockout mice which suggest that phosphatidylcholine (PC) would be a major methyl group acceptor (3). As both Cr and choline (Cho = PC derivatives) are observable by magnetic resonance spectroscopy (MRS), this technique was used to determine whether changes could be measured for each metabolite in the brain of patients affected by such genetic diseases.

METHODS

Eleven young RD patients (median age = 6.5 y, range = 2–22 y) and 36 healthy subjects of similar age (median = 6.9 y, range = 2–18 y) underwent MRS imaging (MRSI) using a 1.5 T Siemens Magnetom Symphony instrument. Data were acquired with point-resolved spectroscopy (PRESS) sequence on a 15 mm thick axial slice passing through the center of the thalami. Acquisition parameters were: field of view (FOV) = 16 x 16 cm^2, voxel size = 15 x 10 x 10 mm^3, 16 x 16 voxels, TE = 135 ms and TR = 1500 ms. Cho and Cr metabolite values were estimated by LCModel in a single voxel from three brain areas in both hemispheres: thalamus, frontal lobe and lenticular nucleus area. Metabolite values were compared between RD patients and control subjects in each brain region using a Student's t test with Bonferroni correction and a *p* value of less than 0.017 for statistical significance.

RESULTS

Average Cho and Cr values and the statistical comparison between RD patients and control subjects are presented in Table 1. A statistically significant decrease in the Cho was measured in the three brain areas. Cr was lower in patients than in controls in the three regions examined but the reduction was not statistically significant.

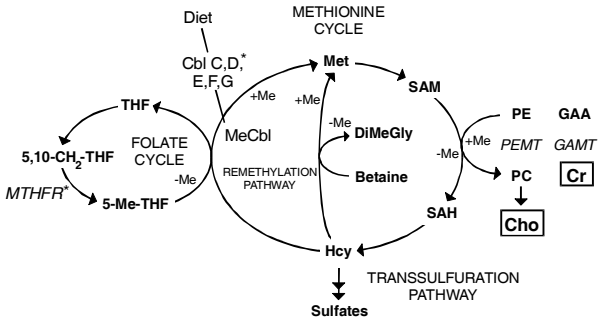

Fig. 1. Methionine metabolic cycle affected by genetic deficiencies (*) impairing the remethylation pathway.

Table 1: Metabolite values for RD patients vs control subjects

Brain region	Metabolite	Control subjects	RD patients	p	Δ (%)
Frontal	Cho	0.064 ± 0.010	0.052 ± 0.009	0.002	-19
	Cr	0.158 ± 0.032	0.140 ± 0.024	0.1	-11
Thalamic	Cho	0.071 ± 0.007	0.064 ± 0.009	0.007	-10
	Cr	0.173 ± 0.019	0.161 ± 0.023	0.09	-7
Lenticular nucleus	Cho	0.069 ± 0.009	0.056 ± 0.010	< 0.0005	-19
	Cr	0.213 ± 0.022	0.203 ± 0.031	0.2	-5

DISCUSSION

The present results demonstrate brain Cho is predominantly affected in patients with RD, suggesting that PC is an important methyl acceptor. This finding is in agreement with recent animal studies (3) but contradicts traditional belief that only Cr is involved. The significant role of Cho could have implications for treatment strategies of RD patients.

References

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