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The Effect of Methionine Synthase Heterozyous Deficiency and Vitamin B_{12} Deficiency on One-Carbon Metabolism of Mice

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B_{12}-dependent Methionine synthase (MS) catalyzes the methylation of homocysteine (Hcy) to methionine using 5-methyl-THF as substrate and regeneration of THF. This enzyme has a crucial role in maintaining intracellular methionine and the folate pool at optimal levels and plasma Hcy at a low level. Deficiency of MS activity in *cblG* patients has been shown to lead to early-onset biochemical phenotype includeing hyperhomocysteinemia, homocysteinuria, and hypomethionemia, and clinical symptoms including megaloblastic anemia, severe developmental delay, ataxia, cerebral atrophy, neonatal seizures, and blindness. Elevated levels of Hcy are correlated with cardiovascular disease and neural tube defects.

The MS knockout mouse has recently been developed. Homozygous MS knockout embryos survived through implantation but die in early embryonic stage. The heterozygous knockout of methionine synthase in mice has been shown to elevate plasma Hcy moderately compared to wild type animals.

MS knockouts may be impaired in their function to remethylate Hcy and also to regenerate non-methyl folate from 5-methyl THF. Because MS is the only known enzyme to regenerate THF, deficiency of the functional form of folate coenzyme including 5,10-methylene THF (which is "methyl folate trap") in MS knockouts may result in the biochemical changes including hyperhomocysteinemia.

Methionine is a precursor of S-adenosylmethionine (S-AdoMet) which is known as a strong activator of cystathionine β-synthase. Therefore impaired do novo methionine synthesis by MS knockout will lead to the depression of S-AdoMet and the Hcy accumulation because of unstimulated cystathionine β-synthase.

We hypothesized that the elevated plasma Hcy in MS heterozygotes is associated with the deficiency of functional folate by methyl folate trap and the depression of S-AdoMet synthesis and the biochemical alteration by MS knockout deficiency may be more susceptible to dietary B_{12} deficiency. We have investigated the metabolic effects of heterozygous MS deficiency and/or B_{12} depletion on one-carbon metabolism in male and female mice by analyzing plasma Hcy, intracellular S-adenosylhomocysteine (S-AdoHcy) and S-AdoMet, plasma and intracellular folate, and MS activity.

In this study, plasma Hcy ($p < 0.05$) and brain S-AdoHcy ($p < 0.05$) were slightly elevated in MS heterozygous mice, but this heterozyous knockout effect was observed only in B_{12} deficient mice. Plasma Hcy and brain S-AdoHcy levels were positively correlated ($\gamma = 0.685$, $p < 0.05$). Plasma folate was elevated by MS heterozygous deficiency ($p < 0.01$) or B_{12} deficiency ($p < 0.05$), whereas hepatic folate was not changed by MS heterozygosity or B_{12} deficiency. These results suggest that a "methyl folate trap" due to MS heterozygosity or vitamin B_{12} deficiency lead to an accumulation of 5-methyl-THF and Hcy in plasma.

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