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CHANGES OF HOMOCYSTEINE AND RELATED COMPOUNDS IN DOWN SYNDROME

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Aim of the study: Down's syndrome (DS) is of interest for the study of neurodegeneration because DS people develop dementia and neuropathological symptoms of Alzheimer's disease. The gene for cystathionine β-synthase (CBS) is located on chromosome 21 and is overexpressed in children with DS. The metabolism of sulfur amino acids could probably be the source of the toxic compound. In the present study, we focused on a single gene on chromosome 21 coding for the enzyme CBS and on its indirect impact on one-carbon metabolism in children with DS. To define the specific imbalances induced by CBS overexpression, plasma levels of relevant metabolites were measured in children with DS and were compared to those from healthy controls.

Methods: We measured plasma total homocysteine (tHcy), methionine (Met), cystathionine (Cystat), cysteine (Cys), and total GSH in 20 children with DS aged between 0.2 to 2.0 years (A) and in 17 children with DS aged between 12.0 to 18.0 years (B) and compared their values with those of 34 healthy children divided into two aged groups as above. Plasma amino acids and amino-thiol-acids were determined by HPLC system.

Results: The children with DS had significantly altered plasma levels of each of the metabolites in the Met/tHcy pathway and also in the CBS-mediated transsulfuration pathway. Plasma Hcy in DS children was 70-76% of that of the healthy children and a marked decrease (-52%) was observed for plasma Met concentration. Plasma levels of Cystat and Cys were significantly increased, consistent with an increase in CBS activity. The reduced plasma GSH observed in the children with DS most likely reflects a situation-linked antioxidant response to chronic oxidative stress, resulting from Cu-Zn superoxide dismutase overexpression.

Conclusions: These preliminary results indicate that in DS children CBS overexpression indirectly deprives the methionine synthase of the tHcy, while, at the same time, it creates "the methyl trap" and supports the increase of the Cystat and Cys levels. It is noteworthy that CBS is continously and strongly expressed in the CNS of human embryos from the earliest stage studied. CBS also has another enzymatic activity, the production of H_2S from Cys. Thus hyperproduction of H_2S secondary to overexpression of the CBS gene in DS could induce dysfunction in muscle (hypotonia) and in brain (mental retardation). Further studies are necessary to verify these hypotheses in DS children.