POSTERS

RESILIENCE ASSOCIATED WITH DEFECTS IN VITAMIN B12 METABOLISM: BALANCING BETWEEN HOMEOSTASIS AND DISEASE

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CblC deficiency is an inborn error of intracellular Vitamin B12 (B12) metabolism caused by loss-of-function mutations in the MMACHC gene leading to metabolic decompensation, including homocysteine (Hcy) accumulation [1,2]. Cognitive impairment and variable disease onset among patients with identical mutations[1,3] motivates investigation of Hcy effects in a neural-like model and supports the concept of metabolic resilience, whereby cells maintain function despite biochemical defects [4].

SH-SY5Y neuroblastoma cells were cultured in B12-deprived media, differentiated into a neural-like phenotype, then exposed to increasing Hcy concentrations and recovered in unsupplemented or B12-supplemented conditions. This approach defined cytotoxic Hcy levels and explored changes in metabolomics, oxidative stress and protein and DNA methylation.

Hcy induced dose-dependent cytotoxicity, with significant effects at higher doses, while B12 partially rescued viability. ^{1}H-NMR metabolomics identified key alterations. Exploratory analyses revealed compartment-specific methylation changes on a proteic level and treatment-specific DNA methylation changes.

These findings support the concept of a metabolic tipping point, where Hcy-induced stress reveals limited resilience. Overall, this study highlights the interplay between metabolic imbalance, protein and epigenetic modulation in neural dysfunction.

References

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