Nitric Oxide Supplementation Treats Common Metabolic Disease

Apr. 26, 2012 — A team of researchers has discovered a treatment for a common metabolic disorder. The study, published by Cell Press on April 26th in the *American Journal of Human Genetics,* the official journal of the American Society of Human Genetics, reports that supplementation of nitric oxide (NO) in mice and man afflicted with argininosuccinic aciduria (ASA), a urea cycle disorder (UCD), results in long-term heart and neuropsychological improvements.

UCDs are genetic metabolic conditions resulting from a deficiency in any of the enzymes of the urea cycle, which takes place primarily in the liver and is responsible for removing ammonia (a toxic nitrogen compound) from the blood stream. When this cycle cannot proceed normally, ammonia accumulates in the blood and damages the liver and nervous system. ASA is the second-most-common UCD and is caused by a deficiency in arginosuccinate lysase (ASL), the only mammalian enzyme able to generate arginine, a precursor for the synthesis of many metabolites, including nitric oxide (NO). People with ASA often have a complex clinical phenotype even in the absence of ammonia accumulation. "Thus, we hypothesized that some of the long-term complications of ASA may result from NO deficiency rather than from ammonia accumulation," explained Dr. Lee, a leading author of this study.

By developing a mouse model of ASA, Lee, Erez, and their team were able to test this hypothesis. Using cutting-edge gene therapy technology, they corrected the urea-cycle defect in the liver and normalized growth and survival of the mice. However, the GT-treated ASA mice remained hypertensive because they required ASL for NO production in the vasculature. Supplementation of NO treated these other disease symptoms in the mice.

"Importantly, we show the translatability of our findings to humans, as we show that treatment with an NO source led to sustained normalization of blood pressure in an ASA subject," said Dr. Lee. "Our data show that ASA is a human genetic model of NO deficiency and that NO supplementation in ASA subjects should be further investigated," he said.

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Journal Reference:

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