Treatment of AHDS with chemical or pharmacological chaperones

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Mutations in the thyroid hormone transporter MCT8 prevent appropriate entry of thyroid hormones into brain cells during development and cause severe mental retardation in affected patients. Current treatment options are thyromimetic compounds that enter the brain independent of MCT8. Some MCT8 deficient patients (e.g. those carrying $MCT8^{delF501}$) are not as severely affected as most others suggesting residual activity of mutant transporters. We showed that $MCT8^{delF501}$ protein has decreased protein stability, but significant residual function once it reaches the plasma membrane. We were able to rescue protein expression and function of $MCT8^{delF501}$ in a MDCK1 cell model by application of the chemical chaperone sodium phenylbutyrate (NaPB), a drug that has been used to treat children with cystic fibrosis and urea cycle defects over extended periods of time. More recently, we were able to extend our previous study and report on the NaPB dependent rescue of a series of other pathogenic MCT8 mutants that are associated with milder patient phenotypes (e.g. $MCT8^{S194F}$, $MCT8^{S290F}$, $MCT8^{L434W}$, $MCT8^{R445C}$, $MCT8^{L492P}$ and $MCT8^{L568P}$). To our surprise, NaPB also mediated rescue of some pathogenic MCT8 mutations that lead to a severe phenotype (e.g. $MCT8^{P321L}$). We now investigate whether NaPB acts not only as a chemical chaperone preventing degradation of mutant protein, but also as an activator of protein function.