Pharmacological Chaperone-Mediated Rescue of Misfolded Proteins Associated with Genetic Conformational Diseases

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Many human diseases result from mutations in specific genes. Once translated, the resulting aberrant proteins are often functionally competent and produced at normal levels. However, because of the mutations, the proteins are recognized as misfolded by the quality control system of the endoplasmic reticulum (ER), and as such, are not processed and trafficked correctly, ultimately leading to cellular dysfunction and disease. Small molecule pharmacological chaperones represent a promising new therapeutic approach to treat these genetic disorders. Pharmacological chaperones selectively bind to the mutant proteins and are believed to stabilize a near-native conformation. This stabilization promotes normal trafficking of the mutant protein and allows passage through the ER quality control system, ultimately increasing protein levels and activity in relevant cellular locations and reducing ER accumulation, aggregation and associated cell stress. Partial or complete restoration of normal function by pharmacological chaperones has been shown for numerous mutant proteins, including enzymes, secreted proteins, transcription factors, ion channels and G protein-coupled receptors. This talk will briefly review data that support the use of pharmacological chaperones to treat the most common lysosomal storage disorder, Gaucher disease, which results from mutations in the enzyme β-glucocerebrosidase. Similarly, data supporting the use of pharmacological chaperones to treat X-linked nephrogenic diabetes insipidus, via restoration of mutant V2 vasopressin receptor function, will be reviewed. Lastly, recent data will be presented that demonstrate the potential application of pharmacological chaperones for the treatment of genetic obesity in humans, via restoration of mutant melanocortin 4 receptor function.

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