

Headliners: Autism NIEHS-Supported Research



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Misfolded Protein Presents Potential Molecular Explanation for Autism Spectrum Disorders

De Jaco A, Comoletti D, Kovarik Z, Gaietta G, Radic' Z, Lockridge O, et al. 2006. A mutation linked with autism reveals a common mechanism of endoplasmic reticulum retention for the α , β -hydrolase fold protein family. *J Biol Chem* 281: 9667–9676.

Currently, there is only very limited information available on the etiology and biological basis of the autism spectrum disorders, although mutations in the *neurexin 3* and *neurexin 4* genes have caught researchers' attention in recent studies. Now NIEHS grantees Palmer Taylor and Mark H. Ellisman at the University of California, San Diego, and their colleagues have determined, among other findings, that homologous mutations in the genes encoding butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) cause defects in protein processing and expression similar to those seen with *neurexin 3*, shedding further light on a potential molecular mechanism underlying autism.

The neuroligins, BChE, and AChE are members of the α , β -hydrolase fold family of proteins. The arginine-to-cysteine substitution in the *neurexin 3* mutation was identified in a set of twins, and cell culture studies show most of the expressed protein being retained within the endoplasmic reticulum, suggesting misfolding of the protein. In addition, the small amount of protein that does reach the surface of the cell shows compromised binding affinity for its partner, β -neurexin. Misfolded proteins causing endoplasmic reticulum retention and compromised functional activity are a common consequence of mutations in cystic fibrosis and metabolic diseases with a genetic origin. In the current study, confocal fluorescence microscopy and analysis of oligosaccharide processing were used to ascertain whether the homologous arginine-to-cysteine mutation affected AChE and BChE despite their differing oligomerization states. By inserting homologous mutations in the AChE and BChE cDNAs, the investigators found that the mutation also resulted in endoplasmic reticulum retention of the two cholinesterases and enhanced degradation in the proteasome. The authors speculate that altering intracellular oxidation/reduction parameters may influence proper folding and export of these proteins.

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