

P009 A β peptides bearing the Flemish mutation are more slowly degraded by neprilysin than wild type A β .

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Five point mutations within the amyloid β -protein (A β) sequence of the APP gene are associated with hereditary diseases which are similar or identical to Alzheimer's disease and encode: the A21G (Flemish), E22K (Italian), E22G (Arctic), E22Q (Dutch) and the D23N (Iowa) amino acid substitutions. Although a substantial body of data exists on the effects of these mutations on APP processing, whether or not intra-A β mutations alter degradation of the peptides remains unclear. Neprilysin (NEP), insulin degrading enzyme (IDE) and plasmin each contribute to normal A β catabolism. We therefore examined the ability of these enzymes to degrade cell-derived and synthetic wild type (wt) and mutant A β peptides. We find that each protease is capable of degrading both wt and mutant (aggregate-free) synthetic and cell-derived A β peptides. Moreover, experiments investigating the rates of cleavage of synthetic A β peptides revealed that all peptides are degraded similarly by IDE and plasmin, but that the Flemish peptide was degraded significantly more slowly by NEP than wt or other mutant peptides. This resistance to NEP-mediated proteolysis may represent one mechanism by which the A21G mutation causes increased intracerebral accumulation of A β .