Amyloid-like aggregation of provasopressin in diabetes insipidus and secretory granule sorting

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Aggregation of peptide hormone precursors in the trans-Golgi network is an essential process in the biogenesis of secretory granules in endocrine cells. It has recently been proposed that this aggregation corresponds to the formation of functional amyloids. Our previous finding that dominant mutations in provasopressin, which cause cell degeneration and diabetes insipidus, prevent native folding and produce fibrillar aggregates in the endoplasmic reticulum (ER) might thus reflect mislocalized amyloid formation by sequences that evolved to mediate granule sorting.; Here we identified two sequences responsible for fibrillar aggregation of mutant precursors in the ER: the N-terminal vasopressin nonapeptide and the C-terminal glycopeptide. To test their role in granule sorting, the glycopeptide was deleted and/or vasopressin mutated to inactivate ER aggregation while still permitting precursor folding and ER exit. These mutations strongly reduced sorting into granules and regulated secretion in endocrine AtT20 cells.; The same sequences - vasopressin and the glycopeptide - mediate physiological aggregation of the wild-type hormone precursor into secretory granules and the pathological fibrillar aggregation of disease mutants in the ER. These findings support the amyloid hypothesis for secretory granule biogenesis.
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