Molecular cell pathology of autosomal dominant familial neurohypophyseal diabetes insipidus

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ABSTRACT

The present PhD study was carried out at the Paediatric Research Laboratory, Aarhus University Hospital, Skejby Sygehus in collaboration with Research Unit for Molecular Medicine, Skejby Sygehus and Department of Human Genetics, University of Aarhus.

Autosomal dominant familial neurohypophyseal diabetes insipidus (adFNDI) is characterized by polyuria, polydipsia, and a deficient secretion of the antidiuretic hormone, arginine vasopressin (AVP). The disease has been linked to mutations in the AVP gene encoding the AVP pre-prohormone. It is largely unknown how mutations in only one allele of gene result in severe AVP deficiency.

The hypothesis of the present PhD study is that the dominant negative effect exerted by the mutations is due to the production of a mutant AVP prohormone, which fails to fold properly and, as a consequence is retained by the protein quality control machinery in the endoplasmic reticulum (ER). This results in accumulation of mutant protein in the ER and initiation of cellular processes leading to degeneration of the AVP producing neuron.

To characterize the molecular mechanisms underlying the development of adFNDI, we have performed genetic analysis of members of fifteen kindreds and characterized the effect of mutations in the AVP gene on the cellular handling of the prohormone by expression studies in neuronal cell lines.

We report seven different previously described mutations in nine kindreds. In each of the other six kindreds, we report unique and novel mutations. The findings both confirm and further extend the adFNDI mutation pattern suggesting that they all affect amino acid residues important for proper folding and/or dimerization of the AVP prohormone. Our expression studies further support the hypothesis as mutations associated with adFNDI and not arFNDI (autosomal recessive FNDI) result in reduced AVP prohormone processing and secretion probably due to retention in the ER.

This PhD dissertation has contributed to the understanding of the molecular mechanisms leading to the development of adFNDI and suggests that expression studies in neuronal cell lines are a suitable model system for examining dominant negative mutations, the effect of such mutations on the folding of hormone precursors in the ER, and the role of the protein quality control machinery in the cellular handling of misfolded protein. Future investigations in this particular system, and in others, could not only reveal the molecular processes leading from ER retention to neuronal cell death in adFNDI but also provide a basis for the understanding of other conformational neurodegenerative diseases like Huntington's, Alzheimer's, Parkinson's, and Creutzfeldt-Jakob disease.