Unfolded protein response in Huntington's disease

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Research question and background

The unfolded protein response (UPR) is a protein quality control mechanism that protects cells against endoplasmic reticulum (ER) stress. Previous studies in our group and others have demonstrated involvement of the UPR in Alzheimer's disease (AD) and other tauopathies. UPR markers (e.g. Bip, pPERK, and pIRE1) were found in pre-tangle neurons containing hyperphosphorylated tau. In literature, in vitro studies suggest that the UPR is involved in models for Huntington's disease (HD). So far there is no data about UPR activation in brain tissue derived from HD patients. In this project we will study the role of UPR activation in affected brain tissue derived from HD patients and the possible relationship with tau pathology in HD. This will contribute to the elucidation of the role of UPR activation in neurodegeneration.

Methods and tissues used

Immunohistochemistry will be used to assay the activation of the UPR and the presence of tau pathology in post-mortem brain tissue derived form patients with HD (striatum). Specific antibodies for UPR proteins will be used. These antibodies have been extensively studied on AD brain tissue.

Results and conclusion

We observed increased presence of UPR markers in HD striatum compared to non-neurological control cases, suggesting that at least some parts of the UPR pathway are activated during HD pathogenesis. In addition, we could show that HD patients have higher levels of the 4-repeat tau isoform and observed a new type of tau pathology, i.e. tau positive nuclear rods, that occur specifically in affected brain regions of HD patients. In conclusion, we found that the UPR is activated in HD and that HD is new type of tauopathy.