Imaging Mutant Huntingtin Aggregates using [^{18}F]CHDI-650 PET in a preclinical model of Huntington's disease

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Huntington's disease (HD) is a fatal neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin gene (*HTT*) that encodes pathogenic mutant huntingtin (mHTT) protein. Therapeutic strategies aimed at lowering mHTT would benefit from non-invasive PET-based methods to evaluate treatment response. The CHDI foundation developed the first-generation PET ligands labelled with ^{11}C, which advanced to clinical evaluation. Further optimization generated an ^{18}F radioligand with improved metabolic stability, brain exposure and specificity, shown by PET imaging in wild-type mice and autoradiography in HD brain samples[1,2]. Here, we characterised the PET radioligand [^{18}F]CHDI-650 in the R6/1 mouse model of HD to assess its sensitivity for monitoring treatment response of mHTT lowering therapies.

[^{18}F]CHDI-650 was produced according to an established method[3] using a TRACERlab system. Radiochemical purity/molar activity of the final [^{18}F]CHDI-650 product was detected by reverse-phase HPLC analysis. Dynamic PET imaging was conducted using R6/1 mice and wild-type littermates at various disease stages. Image processing and kinetic modelling (2TCM) analysis were performed using PMOD software. Ex vivo brain radioactivity was measured using gamma counting. Brains were cryo-sectioned and processed for immunofluorescence to identify HTT load.

[^{18}F]CHDI-650 was produced (1.3 ± 0.2 GBq) with an average radiochemical purity of 99.9 ± 0.1 % and a molar activity of 32.4 ± 5.2 GBq/μmol (n = 9). The radioligand was able to discriminate R6/1 HET from WT mice at an early presymptomatic age for both dynamic PET imaging (striatal) and ex vivo whole brain gamma. A well-defined age associated increase was also evident using both measures. Dual immunofluorescence spatially defined the level of aggregated HTT in striatal and hippocampal regions across the age groups.

[^{18}F]CHDI-650 PET shows great potential as a non-invasive tool for visualising the development of mHTT pathology and as a biomarker for preclinical efficacy studies.

References:

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