Endocannabinoid Neuroenzyme PET Imaging in Huntington's Disease mice

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Huntington's disease (HD) is an autosomal dominant, progressive, neurodegenerative disorder characterized by CAG triplet repeat expansion in the Huntingtin (HTT) gene. This genetic mutation causes the formation and aggregation of the mutant Huntingtin protein, leading to neurotoxicity. Clinically, HD is characterized by movement disorders, dementia, and behavioral and psychiatric manifestations. No effective treatment for HD has been demonstrated to date. Once people with HD receive their diagnosis, there is little hope. Research on new diagnostic and therapeutic targets is essential to better understand the mechanisms of HD. Current work specifically focuses on the endocannabinoid α/β-Hydrolase Domain 6 (ABHD6). The role of ABHD6 in HD pathogenesis remains unclear, however its inhibition has been shown to improve motor coordination symptoms in a HD mouse model. Our research aims to further investigate changes in ABHD6 levels in the zQ175DN mouse model of HD using the ABHD6-targeting radiotracer [18F]JZP-MA-11 for positron emission tomography (PET), a non-invasive in vivo imaging technique. Specifically, we set three key objectives. Objective (1) is the implementation of the novel [18F]JZP-MA-11 radiotracer at our radiopharmacy department. Objective (2) is to determine the optimal kinetic modeling approach for [18F]JZP-MA-11 and to validate the ability of [18F]JZP-MA-11 PET to detect ABHD6 levels in wild-type mice. Lastly, objective (3) focuses on in vivo [18F]JZP-MA-11 PET in heterozygous zQ175DN mice and wild-type littermates to assess ABHD6 levels in the brain, more specifically in the striatum, motor cortex, hippocampus, thalamus and cerebellum. Several timepoints will be investigated (age 3, 6, 9, and 12 months). By exploring ABHD6 in HD, we strive to make meaningful steps in HD research and offer hope to patients and their families.