World Academy of Science, Engineering and Technology
International Journal of Nuclear and Quantum Engineering
Vol:16, No:03, 2022

Development of Positron Emission Tomography (PET) Tracers for the in-Vivo Imaging of α-Synuclein Aggregates in α-Synucleinopathies

Authors : Bright Chukwunwike Uzuegbunam, Wojciech Paslawski, Hans Agren, Christer Halldin, Wolfgang Weber, Markus Luster, Thomas Arzberger, Behrooz Hooshyar Yousefi

Abstract : There is a need to develop a PET tracer that will enable to diagnosis and track the progression of Alpha-synucleinopathies (Parkinson's disease [PD], dementia with Lewy bodies [DLB], multiple system atrophy [MSA]) in living subjects over time. Alpha-synuclein aggregates (a-syn), which are present in all the stages of disease progression, for instance, in PD, are a suitable target for in vivo PET imaging. For this reason, we have developed some promising a-syn tracers based on a disarylbisthiazole (DABTA) scaffold. The precursors are synthesized via a modified Hantzsch thiazole synthesis. The precursors were then radiolabeled via one- or two-step radiofluorination methods. The ligands were initially screened using a combination of molecular dynamics and quantum/molecular mechanics approaches in order to calculate the binding affinity to a-syn (in silico binding experiments). Experimental in vitro binding assays were also performed. The ligands were further screened in other experiments such as log D, in vitro plasma protein binding & plasma stability, biodistribution & brain metabolite analyses in healthy mice. Radiochemical yields were up to 30% - 72% in some cases. Molecular docking revealed possible binding sites in a-syn and also the free energy of binding to those sites (-28.9 - -66.9 kcal/mol), which correlated to the high binding affinity of the DABTAs to a-syn (Ki as low as 0.5 nM) and selectivity (> 100-fold) over Aβ and tau, which usually co-exist with a-synin some pathologies. The log D values range from 2.88 - 2.34, which correlated with free-protein fraction of 0.28% - 0.5%. Biodistribution experiments revealed that the tracers are taken up (5.6 %ID/g - 7.3 %ID/g) in the brain at 5 min (post-injection) p.i., and cleared out (values as low as 0.39 %ID/g were obtained at 120 min p.i. Analyses of the mice brain 20 min p.i. Revealed almost no radiometabolites in the brain in most cases. It can be concluded that in silico study presents a new venue for the rational development of radioligands with suitable features. The results obtained so far are promising and encourage us to further validate the DABTAs in autoradiography, immunohistochemistry, and in vivo imaging in non-human primates and humans.

Keywords : alpha-synuclein aggregates, alpha-synucleinopathies, PET imaging, tracer development
Conference Title : ICNMR 2022 : International Conference on Nuclear Medicine and Radiotherapy
Conference Location : Sydney, Australia
Conference Dates : March 28-29, 2022