Development of selective tau and MAO-B PET tracers through compound optimization of ^{18}F -THK5351

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Background/Aims: Validation studies have shown that ^{18}F -THK5351 PET signal contribute the binding to monoamine oxidase B (MAO-B) and correlates with tau and astrogliosis in neurodegenerative diseases. The aim of study was to develop selective tau and MAO-B PET tracers through compound optimization from ^{18}F -THK5351 to visualize tau pathology and astrogliosis, respectively.

Methods: In vitro competitive binding assay against recombinant MAO-B, MAO-A, and tau aggregates in AD brain homogenates was performed to evaluate binding affinity of test compounds. In vitro autoradiography in frozen human brain tissues was performed using ^{18}F -labeled compounds to evaluate selective binding to each target.

Results: In vitro competitive binding assays demonstrated lower binding affinity of several quinoline derivatives against MAO-B ($K_i > 100 \text{ nM}$) than THK5351. On the other hand, we identified several quinoline derivatives that possess higher affinity against MAO-B than THK5351, but little binding to MAO-A and tau aggregates. Furthermore, in vitro autoradiography of AD brain sections showed the selective binding ability of these compounds to tau protein deposits or MAO-B.

Conclusions: Compound optimization resulted in successful improvement of binding selectivity of quinoline derivatives as tau and MAO-B selective PET tracers, respectively. Selective imaging of tau and MAO-B would be promising markers for monitoring neurodegeneration and neuroinflammatory changes.