Introduction

Despite concerted efforts towards molecular imaging of Alzheimer’s disease (AD) pathologies, early and definitive diagnosis of AD during life remains elusive. Current amyloid and tau imaging approaches lack diagnostic sensitivity and specificity as these abnormal structures also occur in the brains of many cognitively normal individuals (up to 30%).

Molecular imaging of butyrylcholinesterase (BChE) represents an attractive and viable approach for a definitive diagnostic test for AD, as the elevated expression of this enzyme is predominantly associated with pathology in the AD brain rather than cognitively normal individuals.

The synthesis and preliminary in vivo evaluation of an 123I-iodobenzoate single photon emission computed tomography (SPECT) radioligand, TRV6001, is described here.

Methods

TRV6001 Synthesis and Enzyme Kinetics

- Synthesis of TRV6001 followed methods described previously.
- Km, Vmax, and logP values for TRV6001 are indicated in Table 1.
- Specificity of TRV6001 for BChE is indicated in Figure 1.
- Radiochemical yield was ~83% based on HPLC radiogram traces of the reaction mixture.
- Radiochemical purity was ~98% determined by radiochemical TLC experiments.

SPECT/CT/MRI Imaging Protocol

- 5XFAD (n=7) (3APY, 2 PstI mutations), aggressive amyloidosis (+15 months), ii) cognitive impairment and neuronal loss, iii) extensive BChE accumulation with AD pathology.

Wild type (WT) control (n=5).

9-11 month old mice were anesthetized, iV catheter placed in the lateral tail vein and underwent dynamic SPECT imaging for 80 minutes immediately after TRV6001 administration. Mice were subsequently imaged with anatomical computed tomography (CT). A separate magnetic resonance imaging (MRI) scan was performed at 3T to permit regional analysis of the brain.

Results

- There was rapid initial brain uptake of TRV6001 (Figure 3A, B).
- Greater whole brain retention (1.3-2.7 fold) was observed in 5XFAD vs. WT up to 70 minutes post-injection (Figure 3B).
- Sustained cerebral cortex retention (2-3X) greater observed in 5XFAD vs. WT up to 70 minutes post-injection (Figure 4C, A).

Discussion & Conclusions

These preliminary findings provide direct in vivo evidence of TRV6001 crossing the BBB.

Significantly higher cerebral retention of TRV6001 was demonstrated in 5XFAD compared to WT counterparts.

Differential retention in BChE-associated brain structures closely follow the known histochromatographical distribution of BChE in 5XFAD.

Importantly, the cortical retention index showed a significantly greater difference in 5XFAD than WT brains (18-31%) indicating butyrylcholinesterase target engagement by TRV6001.

Rigorous in vivo validation of such BChE-specific radiotracers in animal models should ultimately direct these agents towards clinical trials for the early, definitive diagnosis of AD.

References

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Correspondence

dredebay@dal.ca
sultan.darvish@dal.ca