Preliminary Evaluation of 2-Arylhydroxyquinoline Derivatives for Tau Imaging

VII. 2. Preliminary Evaluation of 2-Arylhydroxyquinoline Derivatives for Tau Imaging

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Introduction

Alzheimer's disease (AD) is a major causative disorder of dementia. In the brains of AD patients, amyloid-β (Aβ) plaques and hyperphosphorylated-tau tangles are observed as characteristic neuropathology of AD. These pathologies are thought to start a gradual accumulation before the onset of clinical signatures of AD. Therefore, the non-invasive quantitative techniques for these pathologies would make an invaluable role to estimation of the severity of AD. We have reported 2-arylquinoline derivatives as tau probes for positron emission tomography (PET)[1,2]. In the optimization of tau probes, the adjustment of lipophilicity of compounds is an important factor which affects the quality of PET images. The purpose of this study was to evaluate the characteristics of novel hydroxyquinoline derivatives with low lipophilicity as tau PET probes[3].

Materials and Methods

Fluorescent staining using AD hippocampal sections was performed in accordance with the regulations of the ethics committee of Tohoku University. The sections were immersed in a 100 μM compound solution containing 50% ethanol for 10 min. Competitive binding assay using [^{18}F]THK-523 and recombinant K18Δ280K tau aggregates was performed as described previously[2]. [^{11}C]THK-951 was radiosynthesized by the reaction of its precursor and [^{11}C]MeOTf. [^{11}C]MeOTf was bubbled through a DMSO solution containing the precursor and tBuOK, followed by heating at 100 °C for 1 min. 2 N HCl was added to the solution and it was heated for 10 min at the same temperature. After

neutralization with 4 N NaOH, the crude mixture was purified by semi-preparative HPLC. *Ex vivo* biodistribution assay in normal mice was performed as described previously[2]. This experiment was approved by the Committee on the Ethics of Animal Experiments at Tohoku University.

Results and Discussion

We synthesized six 2-arylhydroxyquinoline derivatives as tau PET probe candidates (Table 1). In terms of log P values, five of six compounds showed lower lipophilicity (Log P $\leq$ 1.59) than probes which we previously reported[2]. The result of fluorescent staining using AD brain sections is summarized in Table 1. 2-Phenylquinoline derivatives clearly stained tau tangles according with tau immunostaining. The result of competitive binding assay is described in Table 1. Three compounds, THK-951, 14R301 and 14R306, with relatively high log P values showed lower Ki values.

Following these results, we selected THK-951 for biodistribution study. To radiolabel *N*-methyl group of THK-951 with carbon-11, a precursor was reacted with [^{11}C]MeOTf (Fig. 1). [^{11}C]THK-951 was obtained with 39% of radiochemical yield (decay corrected) and higher than 99% of radiochemical purity. The average specific activity of [^{11}C]THK-951 was 83.2 GBq/μmol. To evaluate the brain kinetics of [^{11}C]THK-951, we performed an *ex vivo* biodistribution study in normal mice (Fig. 2). [^{11}C]THK-951 showed a high brain uptake immediately after the injection, and then it was eliminated rapidly from the brain by 30 min post-injection. The radioactivity in the blood also showed a fast clearance. To evaluate the rate of elimination from the brain quantitatively, 2-min-to-30-min uptake ratio was calculated. The ratio of [^{11}C]THK-951 was 21.5 and this value was higher than other THK tau probes[2]. This result suggests that [^{11}C]THK-951 will give high contrast images in the future *in vivo* PET studies in AD human patients or model animals.

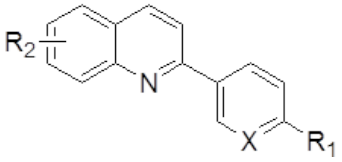
Conclusion

In this study, low lipophilic hydroxyquinoline derivatives were evaluated as candidates of tau PET probes. They showed binding affinity to tau aggregates in the *in vitro* binding assay and fluorescent staining with AD brain sections. [^{11}C]THK-951 was radiosynthesized and its excellent brain kinetics in normal mice was revealed by the *ex vivo* biodistribution study. Future evaluation of [^{11}C]THK-951 and the structural optimization will give the high performance tau imaging technique.

References

1) Okamura N, Suemoto T, Furumoto S, et al., *J. Neurosci.* **25** (2005) 10857.
2) Okamura N, Furumoto S, Harada R, et al., *J. Nucl. Med.* **54** (2013)1420.
3) Tago T, Furumoto S, Okamura N, et al., *J. Label. Compd. Radiopharm.* **57** (2014) 18.

Table 1. Summary of evaluation results of hydroxyquinoline derivatives.



Compound name	X	R_1	R_2	log P	AD tau[a]	Ki (nM)[b]
THK-951	C	$NHCH_3$	7-OH	1.28	++	21
THK-953	N	$NHCH_3$	7-OH	0.56	-	110
THK-5272	C	NH_2	6-OH	0.61	+	36
14R301	C	$NH(CH_3)_2$	6-OH	2.37	++	2.4
14R306	C	$NHCH_3$	6-OH	1.59	+	1.6
THK-5273	N	$NHCH_3$	6-OH	0.90	+/-	30

[a]Results of fluorescent staining assay with AD brain sections.
[b]Results of competitive binding assay.

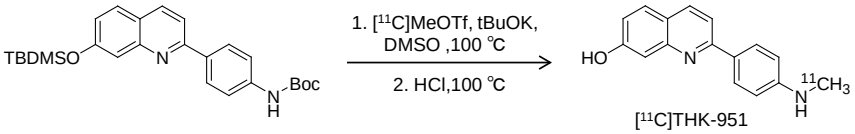


Figure 1. Radiosynthesis of [^{11}C]THK-951.

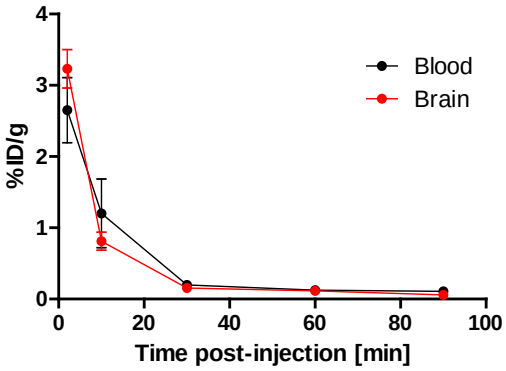


Figure 2. Time-activity curves after intravenous injection of [^{11}C]THK-951 in normal mice. Curves represent the mean value ± SD.