Assessment of (*R*)-^{18}F-OF-Me-NB1 as a potential radiotracer for PET Imaging of the NMDA GluN2B subunit in the monkey brain

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Background

The N-Methyl-D-Aspartate receptor (NMDA) subunit GluN2B is believed to be a therapeutic target for multiple brain diseases, including Alzheimer's disease, schizophrenia and ischemic brain injury. We have previously reported the radiosynthesis and evaluation of racemic and enantiopure (*R*)- and (*S*)-^{18}F-OF-Me-NB1, as well as (*R*)-^{11}C-OF-Me-NB1, in rhesus monkeys for their potential in PET imaging of the GluN2B subunit of NMDA receptor complex (1,2). Here we report a comprehensive evaluation of (*R*)-^{18}F-OF-Me-NB1 as a more promising radiotracer than the S enantiomer.

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Compounds	Ki (nM)	
	GluN2B ([^{3}H]ifenprodil)	Sigma1 ([^{3}H]Pentazocine)
***Rac*-OF-Me-NB1**	37	32
(*R*)-OF-Me-NB1	4	100
(*S*)-OF-Me-NB1	NA	NA

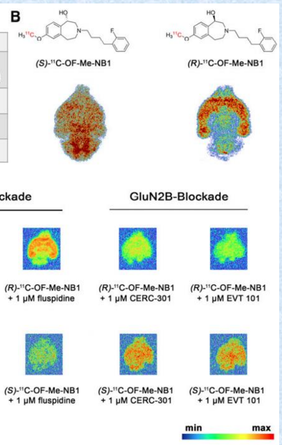

Fig. 1 Binding affinity (Ki) and autoradiography experiments in rodent brain indicate *R*-OF-Me-NB1 is a promising PET tracer for NMDA GluN2B receptor.

References

1. Zheng MQ et al. Journal of Nuclear Medicine 2020, 61 (supplement 1) 265;
2. Haider A, et al. J Nucl Med 2019; 60:259–266

Research Support

1. NIH grant U01MH107803.

Materials & Methods

(*R*)-^{18}F-OF-Me-NB1 was synthesized by ^{18}F-fluorination of a boronate precursor as reported previously (1). PET scans in a rhesus monkey were conducted on the Focus 220 scanner. Blocking studies were also performed after treatment of the animal with the NMDA GluN2B selective antagonist Co101,244, or the sigma-1 receptor selective antagonist FTC-146. Infusion study with displacement of both GluN2B and sigma-1 blockers were also carried out in the same monkey. One-tissue (1T) compartment model and multilinear analysis-1 (MA1) method with arterial input function were used to obtain regional volume of distribution (V_T, mL/cm^3). Occupancy values by the two blockers were obtained by the Lassen plot. Regional non-displaceable binding potential (BP_{ND}) was calculated from the corresponding baseline V_T and the V_{ND} derived from the occupancy plot of the Co101,244 blocking scan.

Metabolite & Input Function

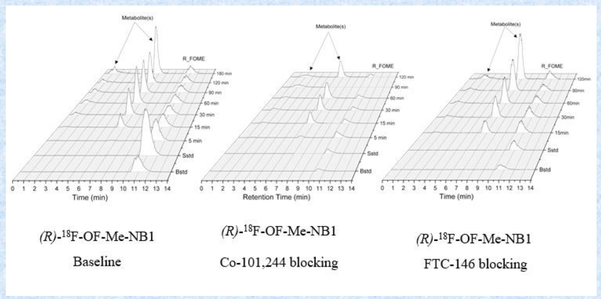

Fig. 2 HPLC profiles for Blood metabolite studies , baseline & blocking

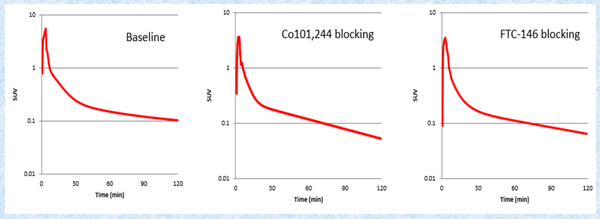

Fig. 3 Arterial Input function curves for baseline and blocking studies.

Results

(*R*)-^{18}F-OF-Me-NB1 was produced in high radiochemical and enantiomeric purity. Metabolism was moderate for all scans, with at least 2 major polar radio-metabolites (Fig. 2). The input function for blocking scans decreased faster than the baseline scan mainly due to the slightly faster metabolism (Fig. 3). In all brain regions it displayed fast uptake and clearance and both blockers reduced brain signals. Blocking with 0.25 mg/kg of Co101,244 resulting in an occupancy of 77% and V_{ND} of 6.36, while 0.027 mg/kg of FTC-146 reduced tracer binding by 30% (Fig.4&5). Both the 1T model and MA1 method gave reliable estimates of regional V_T values, with MA1 V_T ranging from 8.9 in the cerebellum to 12.8 in the cingulate cortex. Regional BP_{ND} ranged from 0.40 in the cerebellum to 1.01 in the cingulate cortex (Table 1). Displacement with Co101,244 significantly reduced the brain uptake but not with FTC-146 during infusion study (Fig. 6)

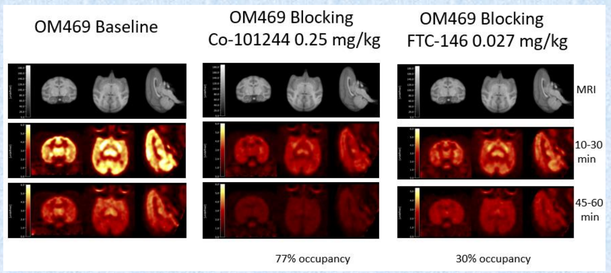

Fig.4 Summed PET images co-registered with MR image in monkey brain

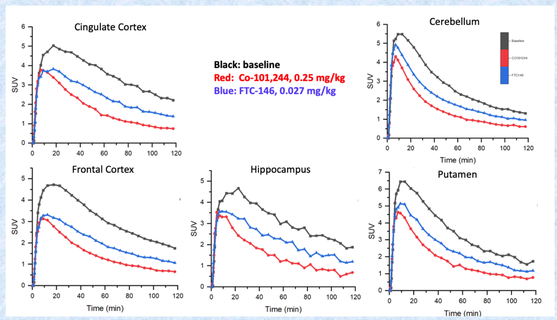

Fig.5 TACs of representative brain regions in baseline & blocking studies

Table 1 MA1-Derived Regional Brain V_T of (*R*)-^{18}F-OF-Me-NB1 in rhesus Monkey

	V_T (mL/cm^3)			
Region of Interest (ROI)	Baseline	Co101,244	FTC-146	BP_{ND}
Cerebellum	8.9	6.9	9.3	0.40
Cingulate cortex	12.8	8.1	11.6	1.01
Frontal cortex	10.7	6.8	9.4	0.68
Hippocampus	11.0	6.9	10.5	0.73
Putamen	11.2	8.1	11.0	0.76
Semiovale	9.1	8.6	9.5	0.43
Thalamus	9.4	6.8	9.4	0.48

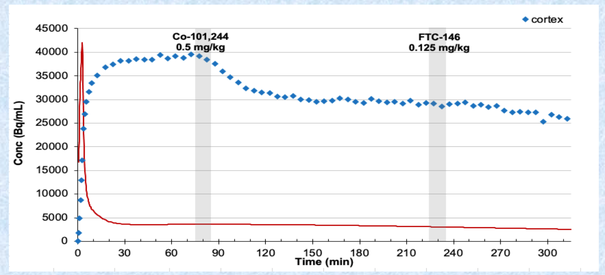

Fig.6 Sequential displacement of (*R*)-^{18}F-OF-Me-NB1 in monkey infusion study

Conclusion

The radiosynthesis and evaluation of (*R*)-^{18}F-OF-Me-NB1 were successfully performed. In rhesus monkeys, (*R*)-^{18}F-OF-Me-NB1 had fast kinetics and heterogeneous uptake across brain regions. Blocking study with GluN2B ligand indicated binding specificity. Value of BP_{ND} were >0.5 in most brain regions, suggesting moderate in vivo specific binding signals. On the other hand, blockable uptake in the cerebellum which lacks GluN2B subunit in adults based on rodent studies and substantial interaction with the sigma 1 receptor raised selectivity issue, which requires further investigation. Taken together, results from our current study demonstrated the potential of (*R*)-^{18}F-OF-Me-NB1 as a useful radiotracer for GluN2B imaging. See **publication #4** and **#46** for more work from our group on this project.

Disclosures

NA