Novel hydroxyl dendrimer-based PET tracer [^{18}F]OP-801 detects early-stage neuroinflammation in 5XFAD mouse model with higher sensitivity than TSPO-PET

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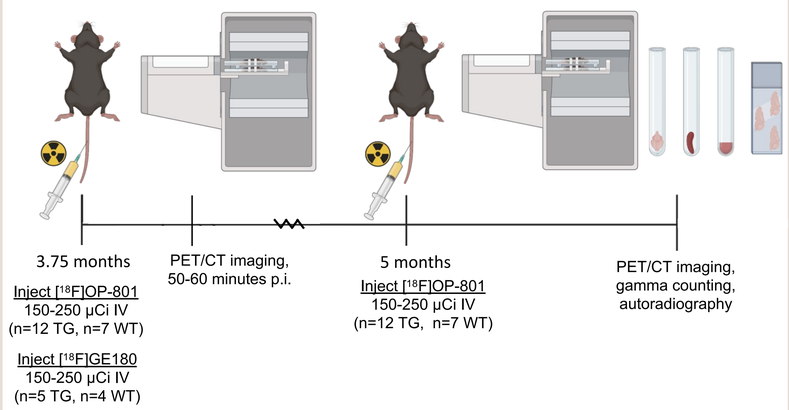
INTRODUCTION

Chronic activation of macrophages and microglia plays a critical role in the onset and progression of neurological diseases, including Alzheimer's. While PET imaging could enable non-invasive visualization and quantification of activated macrophages and microglia *in vivo*, most available PET tracers are nonspecific.[1] To address this need, we developed [^{18}F]OP-801, a synthetic hydroxyl dendrimer-based PET tracer that is selectively (>95%) taken up by reactive macrophages/microglia across the blood-brain barrier.[2] Here, we evaluated the ability of [^{18}F]OP-801 to detect activated macrophages and microglia in the 5XFAD murine model of Alzheimer's Disease compared to an established neuroinflammation imaging approach (translocator protein 18 kDa [TSPO]-PET, using [^{18}F]GE180).

METHODS



Study design illustrates the methods used for this experiment. All mice were either transgenic (TG) or age-matched wild type (WT) 5XFAD female mice.

Image analysis was done using a brain atlas fitted to the CT and co-registered to the summed 10-minute PET images (acquired 50-60 minutes post-injection) in VivoQuant 4.0. Prior to gamma counting (biodistribution), mice underwent cardiac puncture and perfusion, then dissection.

ACKNOWLEDGEMENTS

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REFERENCES

1. Lambert J-C, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nature genetics. 2009.
2. Alnasser Y, et al. Preferential and increased uptake of hydroxyl-terminated PAMAM dendrimers by activated microglia in rabbit brain mixed glial culture. Molecules. 2018.

RESULTS

Image quantification revealed 3-fold higher PET signal in 3.75-months-old TG compared to WT mice using [^{18}F]OP-801, whereas [^{18}F]GE180 signal provided no significant difference in brain regions known to contain activated microglia: cortex and hippocampus (**Figure 1, Table 1**). Significant differences in [^{18}F]OP-801 uptake were observed between 5-months-old TG and WT mice in cortex (p=0.005) (TG: 0.26±0.095%ID/g, WT: 0.11±0.041%ID/g), hippocampus (p=0.017) (TG: 0.18±0.065%ID/g, WT: 0.10±0.026%ID/g) and whole brain (p=0.004) (TG: 0.20±0.082%ID/g, WT: 0.10±0.039%ID/g). TG had almost 5-fold higher [^{18}F]OP-801 signal compared to WT mice (**Table 1**).

	3.75 Months old		5 Months old
	[^{18}F]OP-801 (n=4 WT, n=4 TG)	[^{18}F]GE180 (n=4 WT, n=5 TG)	[^{18}F]OP-801 (n=4 WT, n=4 TG)
Cortex	3.18	1.21	4.75
Hippocampus	3.05	1.24	4.64
Whole Brain	3.14	1.21	4.74

Table 1: Comparison between transgenic (TG)-to-wild type (WT) ratios (equivalent to signal-to-background ratios) in brain regions known to contain amyloid pathology and microglial activation in 5XFAD mice imaged with either [^{18}F]OP-801 or [^{18}F]GE180 at **3.75 months** old.

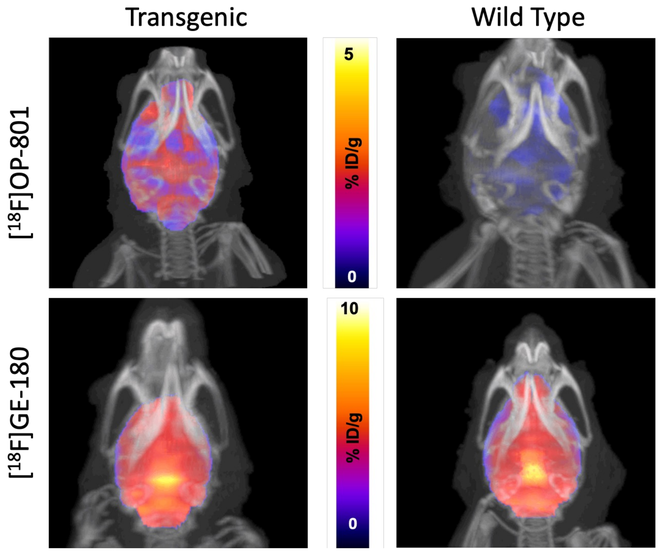


Figure 1: 3D view of representative 3.75-month-old 5XFAD transgenic (TG) and wild type (WT) mouse brain PET images (50–60-minute p.i. summed) using either [^{18}F]OP-801 or [^{18}F]GE180, co-registered with CT images. Image color bars have been scaled for to best enable visualization of each tracer separately.

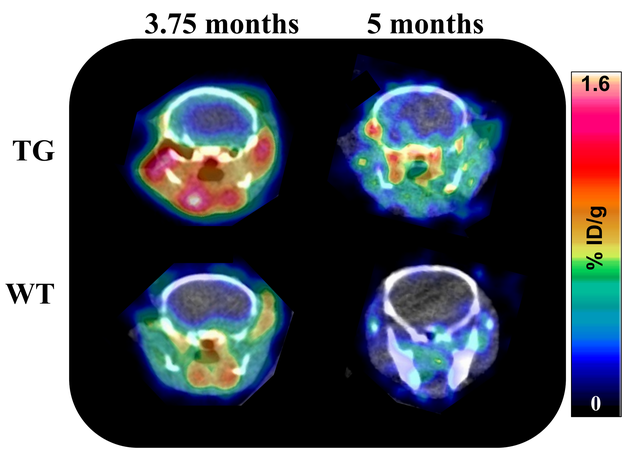
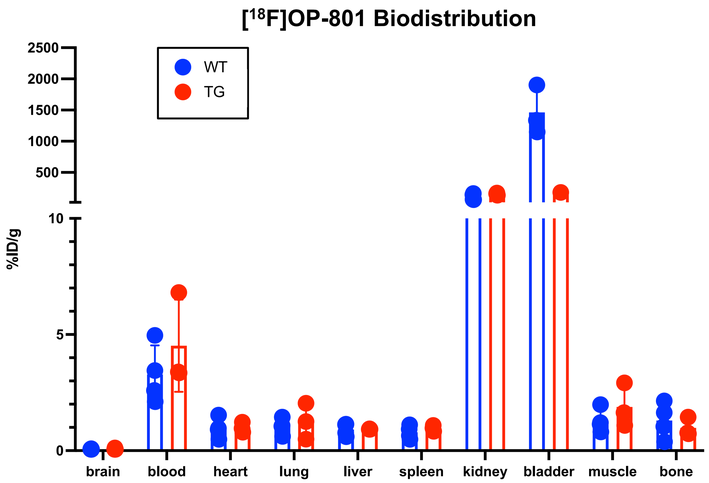
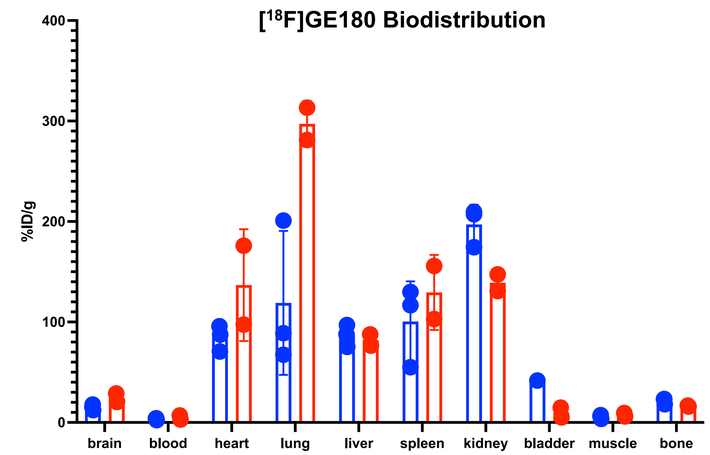


Figure 2 (Left): Representative coronal view of TG and WT mouse brain PET images (50–60-minute p.i. summed) using [^{18}F]OP-801. The same mice are shown at both 3.75 and 5-month-old time points.

Figure 3 (Right): No significant differences were observed between WT and TG %ID/g based on biodistribution in peripheral organs using either [^{18}F]OP-801 (top) or [^{18}F]GE180 (bottom).





SUMMARY

These results suggest that [^{18}F]OP-801 can detect early stage neuroinflammation with higher sensitivity than TSPO-PET. We are currently replicating this study in a larger cohort of 5XFAD mice to correlate PET image findings with immunohistochemistry. [^{18}F]OP-801 is shows promise for visualizing the progression of neuroinflammation with high specificity and sensitivity, warranting further preclinical investigation.