ABSTRACT

The number of individuals with neurodegenerative disorders, particularly Alzheimer's disease (AD), is growing and is projected to continue increasing. Despite this reality, there are no available treatments for AD. Positron emission tomography (PET) imaging has been a valuable tool for drug discovery in the AD space, and has been used to improve our understanding of the pathology of AD. PET imaging strategies in AD have followed the biomarkers used in the drug discovery pipeline, with an early focus on misfolded proteins (amyloid-β (Aβ) and tau neurofibrillary tangles (NFTs)), neurotransmitters, and neuroinflammation. The focus of this thesis has been on using PET imaging to investigate novel aspects of AD pathology. The widely used tau ligand [^{18}F]AV-1451 was investigated for its off-target binding effects to monoamine oxidase (MAO). MAO is also a marker of microgliosis, the activation of microglia, and we have investigated it as an imaging biomarker of neuroinflammation. We developed substrates for imaging MAO-B activity, using a trapped metabolite approach. Inspired by this principle, we used one of these substrates, [^{11}C]AZ, to demonstrate that the feasibility of using an enzyme substrate for dual PET-magnetic resonance (MR) imaging. PET-MR with a single agent has typically been considered impossible because PET imaging would not work at the concentrations required for MRI (i.e. low specific activity). However, we demonstrated that MAO was not saturable *in vivo* at the necessary MR concentration, and that the PET whole brain time activity curves did not suffer. Finally, we evaluated ligands for the receptor for advanced glycation end-products (RAGE), a potential new biomarker of neuroinflammation, using an extracellular and intracellular approach. We evaluated RAGE as a biomarker using the standard lipopolysaccharide (LPS) murine model of neuroinflammation.