Development of PET Probes for Biomarkers of Neuroinflammation

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Abstract

1 in 9 Americans over the age of 65 suffers from dementia. Dementia is an umbrella term for disorders causing cognitive decline, memory lapse, and function impairment. Despite the growing number of people suffering from dementia worldwide, there remains a difficulty in diagnosing and treating these disorders. The most common type of dementia, Alzheimer's Disease (AD) is marked by protein aggregates in the brain: amyloid beta plaques (Aβ) and neurofibrillary tangles (NFT). Although this histology has been known for over a century, the vast body of research surrounding the "amyloid hypothesis" has not resulted in a successful treatment. In response to the many failed drugs that targeted Aβ and NFTs, researchers are turning focus onto alternative theories of cognitive decline. One such theory is neuroinflammation; chronic inflammation in the CNS causes the eventual development of extracellular and intracellular plaques and protein aggregates. In order to visualize this process *in vivo*, I aim to develop PET tracers for biomarkers of neuroinflammation. The process of neuroinflammation begins with the activation of immunocompetent cells in the CNS: microglia. Similar to macrophages in the circulatory system, microglia can be activated into a "M1", pro-inflammatory state. In this state, they influence the excitability of neurons, permeability of the blood brain barrier (BBB), and the activation of astrocytes by excreting pro-inflammatory signals. The morphology of microglial cells change during this activation and present a variety of both overexpressed receptors and intracellular enzymes that may serve as biomarkers. The biomarkers being explored as PET tracer targets in this project are the receptor for advanced glycation end products (RAGE) and monoamine oxidase-B (MAO-B).