Syntheses and Evaluation of GAT-1 Specific PET Probes

Alexandra Sowa
Mentor: Peter JH Scott

Gamma (γ)-amino butyric acid (GABA) is the chief inhibitory neurotransmitter in the body. As such, understanding the distribution of GABA receptors and transporters is necessary to better understand the physiology of the central nervous system (CNS), and the role GABA plays in disease states such as epilepsy, schizophrenia, Alzheimer's Disease, Parkinson's Disease, etc. In the GABAergic system, GABA receptors and transporters are targets for drug development as well as investigated as biomarkers. GABA receptors, located post-synaptically, have been extensively studied and targeted, while the pre-synaptic GABA transporters, specifically GABA transporter 1 (GAT-1), have remained obscure. Although previous mapping studies, *in situ* hybridization, and electron microscopy,[2] have sought to map the distribution of pre-synaptic GAT-1, imaging using positron emission tomography (PET) has the ability to better define the distribution of this transporter. Currently, studies of GAT-1 abundance in disease states is primarily completed with *post-mortem* tissue.[3] Unfortunately, GABA concentrations are known to increase following death, complicating analysis of data obtained from post-mortem studies.[4] PET imaging offers an advanced and non-invasive technique for the analysis of pathophysiological activity in order to narrow down targets and gain unparalleled knowledge about the workings of disease.

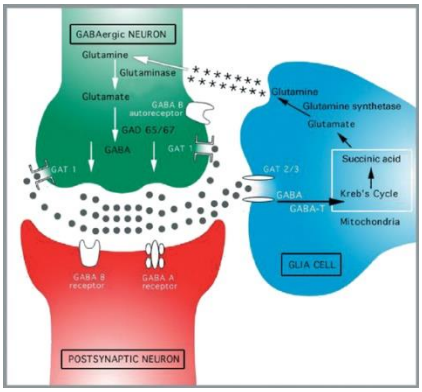

Figure 1: Schematic of a GABAergic synapse. Of note are the $GABA_A$ and $GABA_B$ receptors' post-synaptic position, and GAT-1's pre-synaptic position.

Recently, many groups have concentrated efforts on extensive structure-activity relationship (SAR) studies to develop specific inhibitors of GABA reuptake, *via* targeting of GAT-1. A more recent study by Quandt, *et al*.,[7] produced similarly potent compounds which were also selective inhibitors of GAT-1 Their leads show excellent inhibition of GAT-1 and 15 to 17 fold selectivity over the other GABA transporters (GAT-2, -3, and -4).[7] They are also lipophilic nipecotic acid derivatives, but unlike tiagabine and many molecules based on tiagabine, they are not symmetric. In addition, they contain an aryl fluoride substituent *para* to the ketone, an optimal substitution for ^{18}F-radiolabeling through a nucleophilic aromatic substitution.

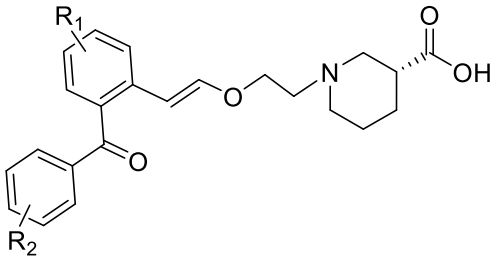

Figure 2: General scaffold of molecules synthesized by Quandt, et al. R1 is F or H, R2 is F, H, Cl or ^{18}F.

Towards these goals, a scaffold has been successfully synthesized and radiolabeled, and initial *in vivo* validation of BBB permeability is underway. Simultaneously, investigation of a second scaffold based on nipecotic acid is being prepared, for investigation as we seek to identify a GAT-1 radiotracer with the characteristics required for eventual transition into clinical studies.