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Invited Perspective

PET imaging of metabotropic glutamate receptor subtype 5 (mGluR5)

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Abstract: Metabotropic glutamate receptors (mGluRs) belong to a family of G-protein coupled receptors involved in the modulation of fast excitatory transmission. In particular, the subtype-5 receptor (mGluR5) was found to be an attractive target for the treatment and diagnosis of variety of psychiatric and neurological disease including anxiety, depression, epilepsy, drug addiction, and Parkinson's disease. Positron emission tomography (PET) is a highly sensitive imaging technique that holds great potential for the diagnosis of a brain disorder. In the study published in the American Journal of Nuclear Medicine and Molecular Imaging, a ^{18}F labelled PET probe was developed targeting mGluR5. This paper represents the efforts and challenges on the design and development of novel PET tracers for mGluR5 imaging.

Keywords: mGluR5, positron emission tomography (PET), ^{18}F, ^{11}C, molecular imaging

Introduction

Glutamate is considered to be a major excitatory neurotransmitter in the central nervous system (CNS). Metabotropic glutamate receptors (mGluRs) are a class of G-protein-coupled receptors that activate intracellular secondary messenger systems when bound by the physiologic ligand glutamate. To date, eight subtypes of mGluRs have been identified, which have been classified into three groups. Activation of Group I mGluRs (mGluR1 and mGluR5) could result in increased calcium release from intracellular stores, which would lead to cell depolarization, enhanced cell excitability, and activation of numerous intracellular signaling molecules [1-3]. Previous studies have shown that mGluR5 is widely distributed within the CNS, including cerebral cortex, dorsal and ventral striatum, olfactory bulb and tubercle, septal area, hippocampus, inferior colliculus, and spinal nucleus of the trigeminal nerve [4-6]. Dysfunction of mGluR5 has been implicated in numerous CNS disorders including anxiety [7], depression [8], epilepsy [9], neuropathic pain [10], drug addiction [11], fragile X syndrome [12] and Parkinson's disease [13]. Therefore, modulation of mGluR5 has great potential for the treatment of these disorders. A noninvasive imaging technique that could investigate the mGluR5 physiological functions under pathologic conditions in patients will be critical for these new therapeutic approaches.

Positron emission tomography (PET) is a highly sensitive non-invasive technique that can be used to image receptor distribution, concentration and functions in normal and pathological states [14, 15]. PET scanning is especially useful in early detection of certain dementias where the damage is too diffuse or the difference is too little to be detected by CT and standard MRI. In order to use PET to identify specific brain receptors (or transporters) associated with particular neurotransmitters, properly radiolabelled receptor "ligands" (PET probes) need to be developed.

Competitive mGluR agonists and antagonists are conformationally constraint glutamate analogs, which competitively interact at the glutamate-binding site. However, these ligands are

not suitable for PET probe development as they lack mGluR subtype-selectivity and often have a low binding affinity. Allosteric modulators of mGluR bind generally in the cell transmembrane domain of the receptor. They have greater subtype selectivity because of the putative heterogeneity of the allosteric sites. Both Negative Allosteric Modulators (NAMs) and Positive Allosteric Modulators (PAMs) of mGluR5 have been developed for the treatment of CNS disorders [16-18]. Based on the mGluR5 allosteric modulators, various novel PET tracers have been synthesized and characterized [19, 20]. Some of these tracers have been tested in animal or even human studies [21-24]. In fact, [^{11}C]M-PEPy and [^{11}C]ABP688 (**Figure 1**) have demonstrated good specific binding towards mGluR5 *in vivo*. Taking advantage of mGluR5 PET tracers, it was demonstrated that mGluR5 was up-regulated in the striatum of parkinsonian primates [25] and down-regulated in the hippocampus of depression patients [24]. Despite their excellent properties as a PET imaging agent in human subjects [26], applications of [^{11}C] labeled PET tracers were limited by the short physical half-life (20 min) of carbon-11. Since [^{11}C]ABP688 has demonstrated promising imaging result *in vivo*, people has been interested in developing its ^{18}F-labeled analog for PET imaging. In this study published in the American Journal of Nuclear Medicine and Molecular Imaging, a ^{18}F labelled analog of [^{11}C] ABP688 was developed and evaluated [27]. This paper provides important guidance on the design and development of novel PET tracers for mGluR5 imaging.

A suitable PET tracer should have reasonable stability in vivo

Although [^{18}F]-PSS223 exhibited high affinity for mGluR5 (3.3 nM, similar to [^{11}C]-ABP688: 1.7 nM) [28], it was significantly metabolized by the rat liver microsomal enzymes or human liver microsomes. As expected, significant amount of defluorination was observed *in vivo*. As the author mentioned, one possible mechanism involves defluorination preceded by the oxygenation of the carbon atom in the a-position to the fluorine atom [29]. In fact, defluorination has been observed in several other PET tracers targeting mGluR5. Unfortunately, *in vivo* defluorination is compound dependent, which make it hard to predict before the tracer was tested *in vivo*. However, this current study did suggest

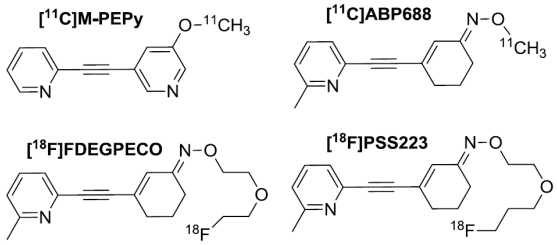

Figure 1. Chemical structures of potential mGluR5 PET tracers.

that microsomal studies *in vitro* might be instructive prior progressing to *in vivo* work.

In vivo test always need to be performed in combination with in vitro assays

Although many PET tracers demonstrated to be a very potent ligand for mGluR5 binding *in vitro*, their *in vivo* characteristics may not be optimal for mGluR5 imaging [30, 31]. Several promising probes targeting mGluR5 were not investigated further as they also accumulate in areas with low mGluR5 expression due to the lack of selectivity *in vivo*. Hydrophobicity of the PET tracer is another factor need to be considered since the tracer needs to diffuse through the blood–brain barrier (BBB). This factor will also affect the brain uptake kinetics of the probe. In fact, the initial rationale to synthesis [^{18}F]-PSS223 is to improve the *in vivo* kinetics of [^{18}F]-FDEGPECO.

Once a proper mGluR5 PET agent was established, much more future investigation is warranted. For instance, multilevel receptor studies on the modulation of dopaminergic and glutamatergic brain function has been performed on parkinsonian rats by combining an mGluR5 PET tracer with other two PET tracers targeting dopamine transporter (DAT) and dopamine D2 receptor [32]. Combining mGluR5 targeted imaging with other receptor studies may lead to a better understanding of pathogenic mechanisms and therapy instruction on CNS disorders.

One disadvantage of using PET for brain imaging is the low spatial resolution. Computed tomography (CT) or Computed Axial Tomography (CAT), Magnetic Resonance Imaging (MRI), Functional Magnetic Resonance Imaging (fMRI) have been extensively used for neuroimaging as well. Combinations of imaging technologies (called multimodality imaging) integrate the

strengths of modalities and eliminate one or more weaknesses of an individual modality. Multimodality imaging has become an attractive strategy for *in vivo* imaging studies owing to its ability for providing accurate anatomical and functional information simultaneously. The anatomical distribution of mGluR5 could be better demonstrated by combining PET with CT, MRI or fMRI. The recent availability of PET/MRI scanner may greatly facilitate this process.

To date, most of the mGluR5 PET tracers are based on Negative Allosteric modulators (NAMs) of mGluR5. However, it was demonstrated that Positive Allosteric Modulators (PAMs) also have potential efficacy in some kinds of CNS disorders [18]. PET imaging studies based on PAMs of mGluR5 are expected in the near future. In addition to CNS disordered, mGluR5 was found to be up-regulated in CNS tumors [33] and some non-CNS tumors [34-37], participating in tumor growth and aggression. mGluR5 could therefore serve as a novel target for tumor imaging and therapy. Clearly, more efforts and reports are expected to develop a successful mGluR5 PET tracer for human use in the near future.

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