Nuclear Medicine and Biology

Editor-in-Chief: William C. Eckelman, PhD

ISSN: 0969-8051

Sjr Info:
https://www.journals.elsevier.com/nuclear-medicine-and-biology

H Index: 74

1.Most Downloaded

^{99m}Tc-labeled PSMA inhibitor: Biokinetics and radiation dosimetry in healthy subjects and imaging of prostate cancer tumors in patients

Abstract

The prostate-specific membrane antigen (PSMA) is expressed in epithelial cells of the prostate and highly overexpressed in 95% of advanced prostate cancers. The aims of this study was to estimate the biokinetics and dosimetry of ^{99m}Tc-EDDA/HYNIC-iPSMA (^{99m}Tc-labeled PSMA inhibitor) in eight healthy subjects and evaluate its usefulness as a tumor-imaging agent in eight prostate cancer patients.

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2.Recent Article

Assessment of PSMA targeting ligands bearing novel chelates with application to theranostics: Stability and complexation kinetics of $^{68}Ga^{3+}$, $^{111}In^{3+}$, $^{177}Lu^{3+}$ and $^{225}Ac^{3+}$

Abstract

Introduction

Recent successes in the treatment of metastatic castration-resistant prostate cancer (mCRPCa) by systemic endoradiotherapy has sparked renewed interest in developing small molecule ligands targeting prostate-specific membrane antigen (PSMA) and chelators capable of stable complexation of metal radionuclides for imaging and therapy. As the size and coordination number of metals for imaging, such as $^{68}Ga^{3+}$, and for targeted therapy, such as $^{177}Lu^{3+}$ and $^{225}Ac^{3+}$, are substantially different, they may show a preference for macrocycles of different denticity. We have prepared three simple conjugates that target PSMA and form radiometal complexes through coordination by either octa-, deca-, or dodecadentate tetraazacyclododecane chelators. The complex formation and metal ion selectivity of these constructs were determined at two relevant temperatures, complex stability was examined in vitro, and tumor targeting was demonstrated in preclinical PCa models with a view towards identifying a candidate with potential value as a theranostic agent for the imaging and therapy of mCRPCa.

Methods

Three bifunctional chelates with high denticity, including the octadentate chelate DOTA, the decadentate 3p-*C*-DEPA and a novel dodecadentate analogue of DEPA, were synthesized and conjugated to a glutamate-urea-lysine (EuK) pharmacophore (EuK-DOTA, EuK-107 and EuK-106, respectively) to enable targeting of PSMA. The metal ion selectivity for each construct was determined by incubation at 25 °C and 95 °C with the trivalent radiometals $^{68}Ga^{3+}$, $^{111}In^{3+}$, $^{177}Lu^{3+}$ and $^{225}Ac^{3+}$. PSMA binding affinity was determined by competitive binding using LNCaP cells, while in vivo tumor targeting of the ^{68}Ga-labeled constructs was examined by positron emission tomography (PET) in LNCaP xenograft tumor-bearing mice.

Results

PMSA affinities (IC_{50} values) were 13.3 ± 0.9 nM for EuK-DOTA, 18.0 ± 3.7 nM for EuK-107 and 42.6 ± 6.6 nM for EuK-106. EuK-107 and EuK-DOTA proved to rapidly and near quantitatively complex $^{68}Ga^{3+}$, $^{111}In^{3+}$, $^{177}Lu^{3+}$and $^{225}Ac^{3+}$ at 95 °C, with EuK-107 also rapidly complexing $^{111}In^{3+}$ and $^{177}Lu^{3+}$ at 25 °C. The inability of EuK-106 to

chelate $^{177}Lu^{3+}$ and $^{225}Ac^{3+}$ suggests that size of the cavity of the macrocylic ring may be more critical than the number of donor groups for the chelation of larger radiometals. In vivo, ^{68}Ga-EuK-107 proved to have similar uptake to ^{68}Ga-DKFZ-PSMA-617, a theranostic ligand currently in clinical evaluation, in a PSMA positive xenograft tumor model.

Conclusions

The broad metal ion selectivity, good in vitro affinity for PSMA and good in vivo tumor targeting suggest that EuK-107, with the 3p-*C*-DEPA chelator, merits further evaluation as a theranostics construct in prostate cancer.

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3.Most Cited

PET imaging with ^{89}Zr: From radiochemistry to the clinic

Abstract

The advent of antibody-based cancer therapeutics has led to the concomitant rise in the development of companion diagnostics for these therapies, particularly nuclear imaging agents. A number of radioisotopes have been employed for antibody-based PET and SPECT imaging, notably ^{64}Cu, ^{124}I, ^{111}In, and ^{99m}Tc; in recent years, however, the field has increasingly focused on ^{89}Zr, a radiometal with near ideal physical and chemical properties for immunoPET imaging. In the review at hand, we seek to provide a comprehensive portrait of the current state of ^{89}Zr radiochemical and imaging research, including work into the production and purification of the isotope, the synthesis of new chelators, the development of new bioconjugation strategies, the creation of novel ^{89}Zr-based agents for preclinical imaging studies, and the translation of ^{89}Zr-labeled radiopharmaceuticals to the clinic. Particular attention will also be dedicated to emerging trends in the field, ^{89}Zr-based imaging applications using vectors other than antibodies, the comparative advantages and limitations of ^{89}Zr-based imaging compared to that with other isotopes, and areas that would benefit from more extensive investigation. At bottom, it is hoped that this review will provide both the experienced investigator and new scientist with a full and critical overview of this exciting and fast-developing field.

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4.Open Access Article

مقاله های زیر بصورت کامل قابل دریافت و درصورت تمایل قابل ترجمه می باشند

Synthesis, radiolabeling and preclinical evaluation of a [^{11}C]GMOM derivative as PET radiotracer for the ion channel of the N-methyl-D-aspartate receptor

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Abstract

Introduction

Presently available PET ligands for the NMDAr ion channel generally suffer from fast metabolism. The purpose of this study was to develop a metabolically more stable ligand for the NMDAr ion channel, taking [^{11}C]GMOM ([^{11}C]**1**) as the lead compound.

Methods

[^{11}C]**1**, its fluoralkyl analogue [^{18}F]PK209 ([^{18}F]**2**) and the newly synthesized fluorovinyloxy analogue [^{11}C]**7b** were evaluated ex vivo in male Wistar rats for metabolic stability. In addition, [^{11}C]**7b** was subjected to a biodistribution study and its affinity (K_i) and lipophilicity($logD_{7.4}$) values were determined.

Results

The addition of a vinyl chain in the fluoromethoxy moiety did not negatively alter the affinity of [^{11}C]**7b** for the NMDAr, while lipophilicity was increased. Biodistribution studies showed higher uptake of [^{11}C]**7b** in forebrain regions compared with cerebellum. Pre-treatment with MK-801 decreased the overall brain uptake significantly, but not in a region-specific manner. 45 min after injection 78, 90 and 87% of activity in the brain was due to parent compound for [^{11}C]**1**, [^{18}F]**2** and [^{11}C]**7b**, respectively. In plasma, 26–31% of activity was due to parent compound.

Conclusion

Complete substitution of the alpha-carbon increased lipophilicity to more favorable values. Substitution of one or more hydrogens of the alpha-carbon atom in the methoxy moiety improved metabolic stability. In plasma, more parent compound was found for [^{18}F]**2** and [^{11}C]**7b** then for [^{11}C]**1**, although differences were not significant. At 45 min, significantly more parent [^{18}F]**2** and [^{11}C]**7b** was measured in the brain compared with [^{11}C]**1**.

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