SELECTIVITY OF THE SIGMA RECEPTOR LIGANDS FOR TUMOR VERSUS INFLAMMATION IN A RODENT MODEL: A COMPARISON WITH FLT AND FDG

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Increased glucose metabolism of inflammatory tissues is the main source of false positive FDG-PET findings in oncology. For this reason, we have tested whether the selectivity of sigma receptor ligands for tumor versus inflammation is higher than that of FDG and FLT. The sigma receptor is strongly over-expressed in a variety of tumors, making it an attractive target for oncology-PET. It has been demonstrated that the receptor density of the sigma-2 subtype shows a high correlation with cellular proliferation rate[1]. Therefore sigma receptor mapping may result in more selective tumor imaging. To test this hypothesis, we compared the biodistribution of [^{18}F]FE-SA5845 (1-(4-[^{18}F]fluoroethoxy-3-methoxyphenethyl)-4-(3-(4-fluoro)-phenylpropyl)piperazine) and [^{11}C]SA4503 ([4-methoxy-^{11}C]1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride) in Wistar rats, which were tumor-bearing (C6 rat glioma in the right shoulder) and also had a sterile inflammation in the left calf muscle (induced by injection of 0.1 ml turpentine). The data were compared with those previously obtained with FDG and another cell proliferation marker FLT[2]. Twenty-four hours after turpentine injection, the rats received an intravenous bolus (10-20 MBq) of either of the two sigma receptor ligands (n=5). The rats were sacrificed after 60 min biodistribution. Tumor/muscle ratios of [^{18}F]FE-SA5845 and [^{11}C]SA4503 were 3.6 ± 1.4 and 4.9 ± 1.6, respectively. These numbers are comparable to a previously reported study[3]. Tumor/muscle ratios of FDG at 2 h post injection (13.2 ± 3.0) were higher, but those of FLT (3.8 ± 1.3) were similar[2]. The sigma receptor ligands did not accumulate in the inflamed tissue. Inflammation/muscle ratios for [^{18}F]FE-SA5845 and [^{11}C]SA4503 were 0.9 ± 0.2 and 1.3 ± 0.4, respectively. For comparison, FDG accumulated in the inflamed muscle, with 4.8 ± 1.2 times higher uptake in the affected thigh than in the contralateral healthy thigh, in contrast to FLT for which this ratio was not significantly different from unity (1.3 ± 0.4)[2]. From these biodistribution data can be concluded that the two sigma receptor ligands have comparable selectivity for tumor versus inflammation as FLT in our animal model, whereas FDG showed both higher uptake in tumor and inflammatory tissue. Further evaluation of the sigma receptor ligands in cancer patients will show whether sigma mapping can be of clinical relevance.

References
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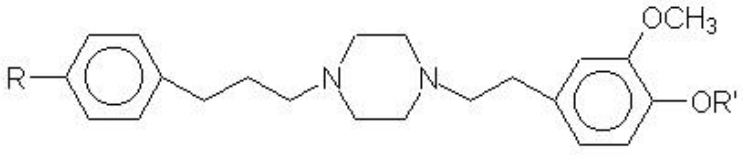

R=H, R'=Me: SA4503
R=F, R'=EtF: FE-SA5845

Keywords: sigma Receptor, Selectivity, Inflammation

NOVEL DOTA CONJUGATED AMINO ACID BRIDGE CYCLIZED ALPHA-MELANOCYTE STIMULATING HORMONE PEPTIDE ANALOGS FOR MELANOMA TARGETING

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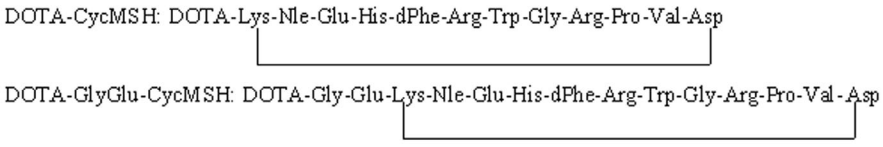
Indium-111 labeled disulfide bond cyclized and non-radioactive rhenium cyclized α-MSH peptide analogs have exhibited high tumor uptake values in B16/F1 murine melanoma mouse model. However, both ^{111}In labeled α-MSH peptide analogs suffered with high kidney uptake or low overall synthetic yield that might impede their clinical applications. **Objectives:** The purpose of this study was to design novel α-MSH peptide analogs cyclized through an amino acid bridge and examine the tumor targeting properties of ^{111}In labeled conjugates in B16/F1 murine melanoma mouse model. **Method:** Two novel amino acid bridge cyclized peptides, DOTA-CycMSH and DOTA-GlyGlu-CycMSH, were synthesized by a solid phase peptide synthesizer, purified by RP-HPLC and labeled with ^{111}In. The tumor trageting properties of ^{111}In labeled α-MSH analogs were determined in B16/F1 murine melanoma bearing C57 mice. **Results:** The tumor uptake values of ^{111}In-DOTA-CycMSH and ^{111}In-DOTA-GlyGlu-CycMSH were 9.53±1.41 %ID/g and 10.40±1.40 %ID/g at 2 hrs post-injection, respectively. The whole-body clearance of the peptides was rapid, with more than 90% of the activity was cleared through urinary system by 2 hrs post-injection. There was little activity accumulated in blood and normal organs except kidney. ^{111}In-DOTA-CycMSH and ^{111}In-DOTA-GlyGlu-CycMSH exhibited peak renal uptake value of 21.69±0.34 %ID/g and 13.07±2.49 %ID/g at 4 and 2 hrs post-injection, respectively. ^{111}In-DOTA-GlyGlu-CycMSH displayed signifcant ($P<0.05$) lower kidney uptake than ^{111}In-DOTA-CycMSH at all time points investigated in this study. **Conclusions:** ^{111}In-DOTA-CycMSH and ^{111}In-DOTA-GlyGlu-CycMSH exhibited high tumor uptake in B16/F1 murine melanoma bearing C57 mice. Introduction of a linker (-GlyGlu-) between DOTA and CycMSH improved kidney clearance of the peptide. ^{111}In-DOTA-GlyGlu-CycMSH exhibited higher tumor uptake and much lower renal uptake than ^{111}In labeled disulfide bond cyclized α-MSH peptide analogs. Although ^{111}In labeled non-radioactive rhenium cyclized α-MSH peptide analogs displayed higher tumor uptake and lower renal uptake than ^{111}In-DOTA-GlyGlu-CycMSH, the promosing pharmacokinetics of ^{111}In-DOTA-GlyGlu-CycMSH highlighted the potential of amino acid bridge cyclized α-MSH peptide analogs as a novel class of peptides for melanoma imaging and therapy.



Keywords: Indium-111 Labeled, alpha-MSH Peptide, Melanoma Targeting

FUTURE QUALITY ASSURANCE STRATEGIES FOR PET RADIOPHARMACEUTICALS AT SUNY BUFFALO

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As the field of PET continues to expand, so do the regulations associated with the manufacturing of the radiopharmaceuticals utilized in this technology. This increased scrutiny can have a serious impact on a PET laboratory in a number of ways. These regulations are being driven by both the FDA as well as the pharmaceutical industry. We will attempt to discuss the strategy our laboratory is using to address these issues. Specific examples will be provided for each area of concern.

In the United States, most groups are aware of a draft of the current Good Manufacturing Procedures (cGMP's) published repetitively over the last number of years. While most facilities have attempted to address many of these guidelines, compliance is not uniform throughout the field. Confusion still exists and the philosophy of most is to wait until regulations are strictly defined and enforced. The European Union has been witness to these regulations.

To date, the major focus has been on operations associated with well-known, established radiotracers (ie. FDG, NH3). While this is a logical first step, a gray area exists when one considers research PET radiopharmaceuticals. Are "NDA-like" operations required for all drugs that are injected into humans? Some will argue yes. If this is the case, then the length of time required to follow strict cGMP's in the synthesis of all radiopharmaceuticals will have an effect on all operations in the PET laboratory.

Issues such as **Material Management** (procedures for receipt, login, handling, testing, approval and rejection of components and reagents), **Compounding** (controlled process, component identification, production procedure verification, action limits, sterilization assurance), **Instrumentation** (logbook documentation, performance verification for components and systems, maintenance, criteria and schedule for PQ), **Analytical Testing** (final product specifications, test validation), and **Quality Assurance Practices** (documentation and verification, batch acceptance/rejection procedures) will be presented.

Initial qualification and annual recertification for all personnel synthesizing compounds involved in human clinical studies will be discussed (such as annual recertification for aseptic technique using media fill). Personnel who have made PET compounds for twenty years will still need to be certified. While one may be certified for general laboratory operations certification will also be on a compound by compound basis.

Several other topics such as an established complaint system, scheduled preventative maintenance (modules and QC instrumentation), documented training of both established and new personnel, environmental testing, and security are also other areas of concern and will briefly be discussed should time/space allow for this.

Keywords: Quality Assurance, Good Manufacturing Practices, Standard Operating Procedures

AN AUTOMATED PNEUMATIC TRANSPORT SYSTEM FOR PET RADIOPHARMACEUTICALS

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A pneumatic transport system was recently established between our cyclotron/ radiochemistry facilities and the PET imaging suites that are separated by a distance of ~2 km. Unique features of this system include a path which crosses a river, a 3-way networked computer control system, and novel carrier designs.

The carriers are moved by pressurized air from behind. The tubing used was 2 inch OD, 1.5 inch ID Polyproplene tube. Automatic full-port ball valves were installed just prior to the loading station, and near the end of the run. The latter valve is used to perform a pressure test to monitor for air leaks in the system. The air pressure at the sending station is maintained near 50 PSI through use of a large capacity pump and two 2000 liter air ballast tanks. The pipe connecting the ballast tanks to the sending station is of larger diameter (3 inch ID). The vertical launch system employs a bayonet-type loading design. At the receiving end, there are air baffle holes placed about 10 m before the end of the tube. After the carrier passes by the baffled region, it is slowed by the buildup of an air cushion in front of the carrier as it drops gently into an end plate. The end plate swivels away to release the carrier from the tube. Interlock switches are placed on the loading door, receiver door, air pressure, valve positions, and an optical sensor that monitors whether the receiver is occupied. All interlocks must be active for the initiation of a transport to occur.

The control system employs three laptop computers. Programming was done using SoftWire programming tools within Visual Basic. The computers communicate to each other through the internet via TCP/IP protocol. A computer at the sending station controls the sending operations. Dose information is entered into the computer or imported from synthesis systems. This information is used to produce a display of real-time activity on all 3 computers in the system. The sending program opens the sending station valve for approximately 40 s, and then closes the valve. The carrier slows over the last portion of its transit, reaching the receiving end at ~90 s. The slow rotation of the ball valve (~7 s to full open) ensures that there is not an abrupt pressure wave that hits the carrier at the sending station. A second computer is located at the receiving station. It monitors activity, provides for additional data entry (e.g. patient identifier), allows the printing of a label for the dose or records, and monitors the occupancy of the receiver tube and door. The third computer is located in the PET scanning room. It displays real-time activity, specific activity, and has a foot switch that is employed to mark the times of tracer administration and blood sample collection. All data is stored on the hard disk. A chat function allows typed messages to be sent between the 3 computers.

The carrier incorporates a sterile 10 mL syringe within a nylon carrier shell (Fig. 1). The plunger stem is cut off before assembly, allowing complete filling of the syringe while maintaining the minimal carrier length. The dose is transferred to the patient through a standard luer extension tubing set without disassembly of the carrier.

A pneumatic transport system has been established for PET radiopharmaceuticals that streamlines data collection, activity and specific activity monitoring and acquisition of injection and blood sample times.

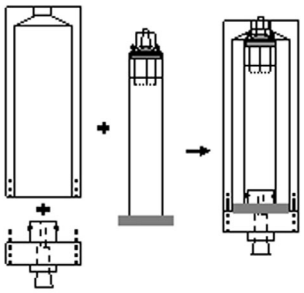

Figure 1. Diagram of pneumatic carrier assembly. O-rings are shown as solid dots in cross-section.

Keywords: PET, Pneumatic, Transport