THE SYNTHESIS AND IN VIVO CHARACTERIZATION OF [^{18}F]FESPARQ, A NEUROKININ-1 (NK1) RECEPTOR PET LIGAND

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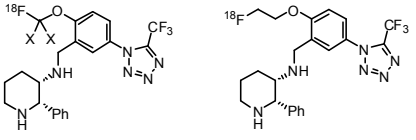
Keywords: NK1, PET, Fluorine-18

[^{18}F]SPARQ (Substance P Antagonist Receptor Quantifier, Figure 1, **1a**, hNK1 IC_{50} = 67pM) is an NK1 receptor PET ligand that was developed in collaboration with the Turku, Uppsala and Hammersmith PET Centers. One drawback of this tracer is its faster rate of defluorination in non-human primates than in humans. It was our desire to improve [^{18}F]SPARQ for preclinical PET studies in non-human primates by slowing the rate of defluorination and increasing the plasma half-life of the tracer. Previously we introduced deuterium atoms in the fluoromethyl methylene group to produce [^{18}F]DSPARQ, **1b**, and more recently we have synthesized the fluoroethyl analog ([^{18}F]FESPARQ, **2**; hNK1 IC_{50} = 17pM).



1a, X=H
1b, X=D

2

Figure 1.

Compound **2** has been evaluated and compared with [^{18}F]DSPARQ, **1b**. Figure 2 shows the time-activity-curves for **1b** (dashed line) and **2** (solid line) in rhesus monkey in the putamen, cortex and cerebellum, showing similar behavior for each tracer. The increasing TAC in the cortex for **1b** is due to its more rapid defluorination and bone uptake, which results in activity spilling into cortical regions. This is absent for **2** due to its slower rate of defluorination. Figure 3 is a comparison of the "chaseability" of **1b** and **2** in rhesus monkey showing, after administration of an unlabelled NK1 antagonist at 180 minutes, **2** responds quicker to the chase and chases more completely than **1b**. Compound **2** has proven to be a useful tracer in preclinical PET studies having the advantage of longer plasma half-life and faster chase from the receptor than **1b**.

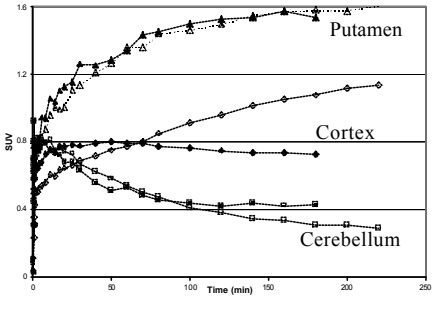


Figure 2.

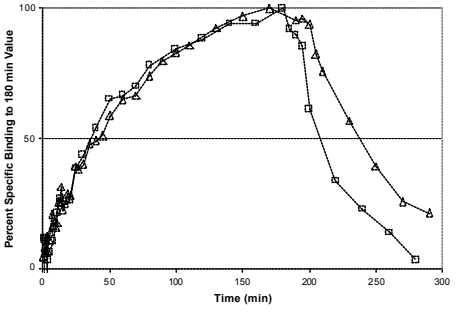


Figure 3.

SYNTHESIS AND BINDING STUDIES OF LIGANDS SELECTIVE FOR DELTA OPIOID RECEPTORS: RADIOIODINATED (*E*)- AND (*Z*)-N1´-(3-IODOALLYL) NALTRINDOLE

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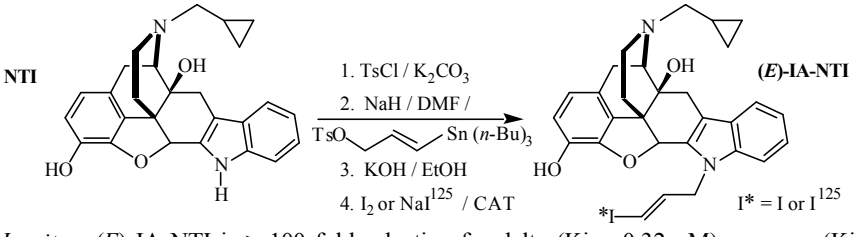
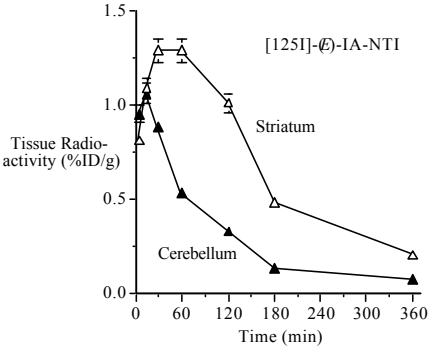
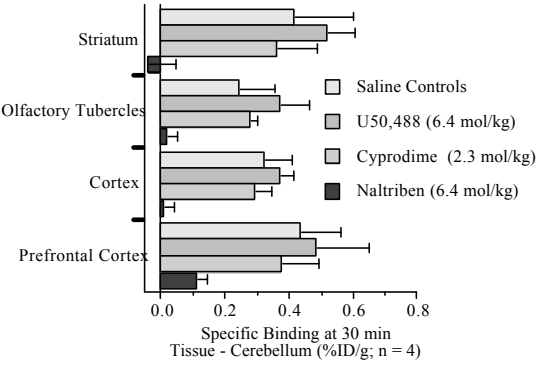
Keywords: opioid receptors, mouse, radioiodine, SPECT

N1´-([11C]-Methyl)naltrindole allows PET imaging of delta opioid receptors in human brain, as well as on the primary tumors of lung and breast cancer patients. We have been interested in the development of radioiodinated delta ligands for complementary SPECT imaging and for laboratory investigations. Previously, we evaluated 7´-iodonaltrindole and its N1´-methyl counterpart radiolabeled with I-125 and I-123. Both compounds showed high affinity and selectivity for binding to delta over mu or kappa sites *in vitro*, but their specific binding to delta sites *in vivo* in mouse brain was low. To identify radioligands with improved specific binding in brain, which also might carry over to studies of receptors on peripheral tumors, we chose to study N1´-iodoallylnaltrindoles (IA-NTI) having either (*Z*)- or (*E*)-configurations. The synthetic route is exemplified below. Electrophilic radioiododestannylation, the final step, takes place under mild, no-carrier-added conditions within one min at room temperature. The geometrically pure (*Z*)- and (*E*)-isomers are produced with high specific activity and in nearly quantitative yield. No complications were noted from protodestannylation or from radioiodination of the phenolic ring.



In vitro, (*E*)-IA-NTI is > 100-fold selective for delta (Ki = 0.32 nM) over mu (Ki = 37.2 nM) or kappa (Ki = 98.1 nM) sites, and is twice as potent as the (*Z*)-isomer (Ki delta = 0.64 nM). [125I]-(*E*)-IA-NTI also exhibited better pharmacokinetic properties *in vivo*, with prolonged retention in striatum, a region rich in delta sites, compared to cerebellum, a region with few delta receptors. As shown below, the radiopharmacology proved consistent with selective localization of delta sites throughout the brain. [125I]-(*E*)-IA-NTI specific binding was blocked (= 0.01) by the delta antagonist naltriben, but not by the mu antagonist cyprodime or the kappa agonist U-50,488.





[^{11}C] KR31173, A NOVEL RADIOLIGAND FOR IMAGING THE AT1 ANGIOTENSIN RECEPTOR WITH PET

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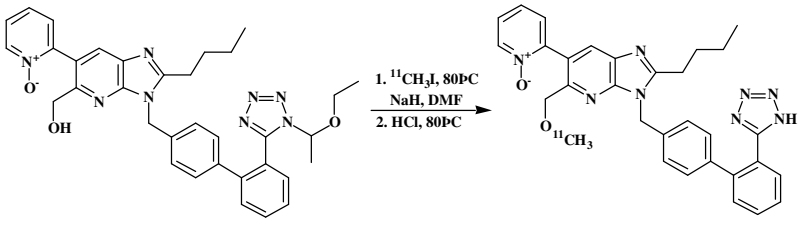
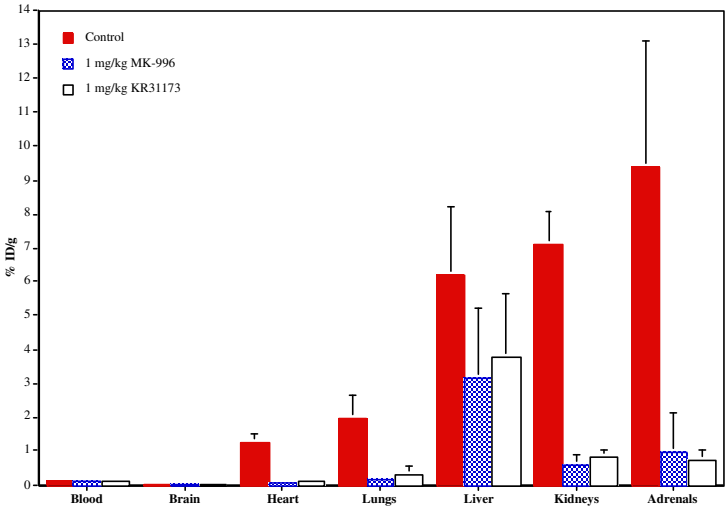
Keywords: Angiotensin, AT1, carbon-11, mice, PET

2-Butyl-5-methoxymethyl-6-(1-oxopyridin-2-yl)-3-[[2´-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl]-3H-imidazo[4,5-b] pyridine (KR31173) was radiolabeled by coupling a tetrazole-protected hydroxy precursor with [^{11}C] methyl iodide and removing the protecting group by acid hydrolysis. The time for synthesis, purification, and formulation was 27 minutes (n=4) with an average radiochemical yield of 6.6% and an average specific activity of 7,758 mCi/µmol at end-of-synthesis.



[^{11}C] KR31173
IC_{50} = 3.27 nM

In mice, the highest uptake of [^{11}C] KR31173 was in the adrenal glands, kidneys, and liver. Tissue to blood ratios were generally greater than 10 to 1. Uptake of the tracer in the adrenal glands, kidneys, lungs, and heart was blocked with a 1 mg/kg dose of KR31173 or MK-996.



This radiotracer is currently being evaluated further by PET imaging of baboons.

[^{11}C]TMSX: AN ADENOSINE A_{2A} RECEPTOR LIGAND FOR MYOCARDIAL IMAGING BY PET

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Keywords: [^{11}C]TMSX, adenosine A_{2A} receptor, heart, PET

Adenosine is an endogenous modulator of synaptic functions in the central nervous system (CNS) as well as in the periphery. Two major subtypes of receptors; adenosine A_1 and A_2 receptors mediated the effects. Recent advances in molecular biology and pharmacology have demonstrated the presence of at least five subtypes i.e., A_1, A_{2A}, A_{2B}, A_3 and A_4 receptors. In the cardiovascular system, the A_{2A} receptors are present on the endothelium and the vascular smooth muscle cells. Previously we have proposed that [7-methyl-^{11}C]-(*E*)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine ([^{11}C]TMSX, Fig. 1) is a potential radioligand for mapping adenosine A_{2A} receptors of the brain by PET (1). Its analogue [7-methyl-^{11}C]-(*E*)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine was the potential myocardial adenosine A_{2A} receptor imaging agent (2). In the present study, we studied the potential of [^{11}C]TMSX for myocardial imaging.

[^{11}C]TMSX was prepared by the [^{11}C]methylation of nor-TMSX with [^{11}C]CH_3I. The myocardial uptake of radioactivity was measured in mice after intravenous injection of [^{11}C]TMSX. Metabolites analysis was performed by HPLC. The blocking effects of carrier TMSX and agonists: A_{2A}-selective CSC, A_1-selective DPCPX and non-selective theophylline, were measured. Myocardial imaging with PET and [^{11}C]TMSX was performed in a volunteer.

After injection of [^{11}C]TMSX the uptake of radioactivity in the mouse heart was high and decreased gradually. In the heart 94% of the radioactivity was detected as an unchanged form 30 min post-injection. The myocardial uptake reduced dose-dependently with cold TMSX and by co-injection of CSC, but not of DPCPX (Fig. 2). Pre-treatment with a high dose of theophilline also reduced the myocardial uptake. The myocardial imaging by [^{11}C]TMSX PET was successfully performed (Fig. 3). In human plasma 94% of the radioactivity was detected as an unchanged form 60 min post-injection.

In conclusion, an adenosine A_{2A} receptor antagonist [^{11}C]TMSX has the potential for myocardial imaging by PET.

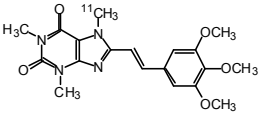

Fig. 1. [^{11}C]TMSX

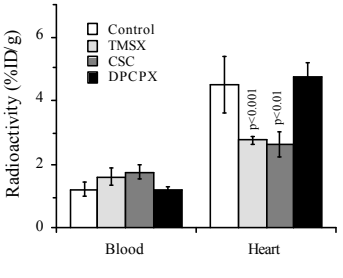

Fig. 2. Effects of co-injection of TMSX, adenosine A_{2A} antagonist CSC or adenosine A_1 antagonist DPCPX.

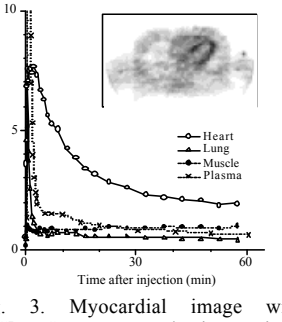

Fig. 3. Myocardial image with [^{11}C]TMSX PET and time-activity curves of in a normal volunteer.

References

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N.C.A. RADIOSELENATION OF AN ADENOSINE-A_1 RECEPTOR LIGAND

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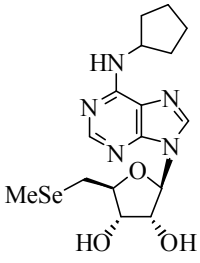
Keywords: Adenosine-A_1 receptor ligand, n.c.a. radioselenation, selenium-73, PET

Adenosine-A_1 receptors are heterogeneously and widely distributed in the central nervous system and are considered to have versatile neuromodulatory functions. The clinical importance with respect to diseases like stroke, dementia, movement disorders as well as involvement in cognitive processes and regulation of sleep makes these receptors attractive targets for *in vivo* radionuclide imaging.

Previously, the partial agonist 5'-(methylseleno)-N^6-cyclopentyladenosine (**1**) has been synthesized, which proved selective for the adenosine-A_1 receptor, displaying an affinity in the nanomolar range using membranes of rat brain cortex (K_i: 76 nM)[1].

1



The positron-emitting radionuclide selenium-73 is an interesting alternative label for application in positron emission tomography. Its physical half-life of 7.1 h permits to follow the biodistribution and kinetics of appropriately selenated radiotracers over extended periods. In order to evaluate the suitability of a new no-carrier-added radioselenation method[2] for this molecule, selenium-75 was used initially to obtain n.c.a. [^{75}Se]**1**.

A polymer-supported reaction starting with n.c.a. $^{75}Se^0$, cyclohexyl isocyanide and aminomethylated polystyrene yielded the corresponding polymer-bound [^{75}Se]selenourea-derivative, which was subsequently alkylated with methyl triflate. The [^{75}Se]selenouronium salt formed was hydrolysed under basic conditions to give n.c.a. methyl[^{75}Se]selenolate. A following alkylation with 5'-bromo-2',3'-isopropylidenedioxy-N^6-cyclopentyladenosine and subsequent deprotection yielded n.c.a. [^{75}Se]**1** with an overall radiochemical yield of 30 % and a radiochemical purity of > 99 % within a total reaction time of 40 min.

Radioligand binding studies for **1** were carried out here also on pig cortical membranes. The affinity of **1** for the adenosine-A_1 receptor was determined by competition with [^{3}H]CPFPX. The K_i value of **1** for the adenosine-A_1 receptor was 0.9 nM (0.8 – 1.1 nM, 95 % confidence interval) in contrast to the previous study[1]. On the other hand, **1** had a K_i value of 1.3 µM (0.3 – 5.5 µM, 95 % confidence interval) for the adenosine-A_{2A} receptor measured by displacement of [^{3}H]CGS21680 from pig striatal membranes. This demonstrates, that **1** is about 1500 fold more selective for the adenosine-A_1 than for the -A_{2A} receptor. These results are now being confirmed by *ex vivo* studies with rats.

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