CHEMICAL DELIVERY SYSTEM OF METAIODOBENZYLGUANIDINE (MIBG) TO THE CENTRAL NERVOUS SYSTEM

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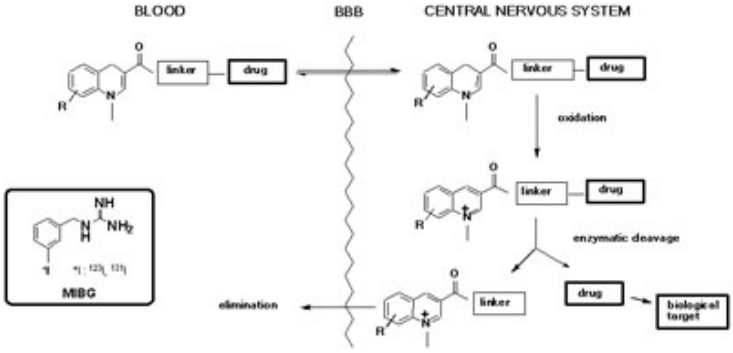
Objectives: A chemical delivery system (CDS) based on a dihydroquinoline / quaternary quinolinium salt redox system analogue to the endogenous NADH / NAD^+ coenzyme system has been successfully used by Bodor and coll[1] to improve the access of therapeutic agents to the central nervous (CNS). The drug is linked to the dihydroquinoline carrier that enables the transport across the BBB where an enzymatic oxidation gives the quinolinium salt. Then, an enzymatic cleavage releases the drug and can reach its biological target. [^{123}I / ^{131}I] metaiodobenzylguanidine (MIBG), a specific tracer of norepinephrine uptake, is widely used for scintigraphic imaging studies of adrenergic tumors[2] (pheochromocytoma, neuroblastoma). As MIBG does not cross the BBB, the dihydroquinoline / quinolinium salt CDS has been applied to achieve its CNS penetration and to study the noradrenergic system into the brain. "



Methods: Compound 1 was synthesized from 3-quinoline carboxylic acid according to a two steps synthesis. After methylation and reduction reactions, the CDS-MIBG 3 wasobtainedas reference compound. Quaternarization of 1 with [^{11}C]methyl triflate followed by reduction of the quaternary salt [^{11}C]2 with BNAH afforded the corresponding 1,4-dihydroquinoline [^{11}C]3. [^{11}C]3 was injected into rats and cerebral samples were analyzed by HPLC and by LC/MS/MS methods. [^{125}I]1 was obtained in a three steps synthesis starting by radioiododestannylation of precursor 4, [^{125}I]NaI and H_2O_2 as an oxidant followed by HPLC purification. The two following steps were done one pot as described for the C-11 labelling affording to [^{125}I]3.

Results: CDS-MIBG 3 wasobtainedwith an overall yield of 29% from 3-quinoline carboxylic acid. The incorporation of [^{11}C] methyl triflate to the quinoline 1 was 95%. Reduction of [^{11}C]2 with BNAH provided [^{11}C]3 with a radiochemical yield of 95%. After HPLC purification and formulation, [^{11}C]3 was obtainedwith a radiochemical purity greater than 99%. After [^{11}C]3 injection into rats, the data obtained by HPLC and LC-MS/MS have shown the penetration of CDS-MIBG [^{11}C]3 into the central nervous system, its oxidation followed by the enzymatic cleavage leading to the release of MIBG. Radioiodinated [^{125}I]3 was obtained in a 24% overall radiochemical yield (60% for the first step and 40% for the last two steps).

Conclusions: Perspectives of this work are dedicated to the in/ex-vivo characterization of [^{125}I]3 in rat brain by biodistribution and metabolite studies.

References: 1- 1-Pro 1-Prokai L, Prokai-Tatrai K, and Bodor N. 2000, Med.Res.Rev., 20, 367 - 416. 2-Eisenhofer G, Bornstein SR, Brouwers FM, Cheung NK, Dahia PL, de Krijger RR, Giordano TJ, Greene LA, Goldstein DS, Lehnert H, Manger WM, Maris JM, Neumann HP, Pacak K, Shulkin BL, Smith DI, Tischler AS, and Young WF. 2004, Endocr.Relat. Cancer, 11, 423 - 436.

BRAIN-SPECIFIC AND POLYFUNCTIONAL DENDRITIC RADIOPHARMACEUTICALS

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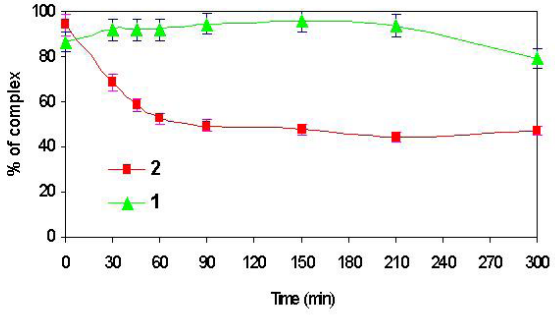
Objectives: Neurodegenerative diseases represent the first cause of mortality in the western countries. The diagnosis of these diseases such as Alzheimer or Parkinson requires contrast agents able to reach the brain by first getting through the Blood Brain Barrier (BBB). Thus, the goal of our research is to adopt a polyfunctional strategy for the elaboration of brain-specific radiopharmaceuticals by means of chemical engineering and, in particular, a 'dendrimer' approach.

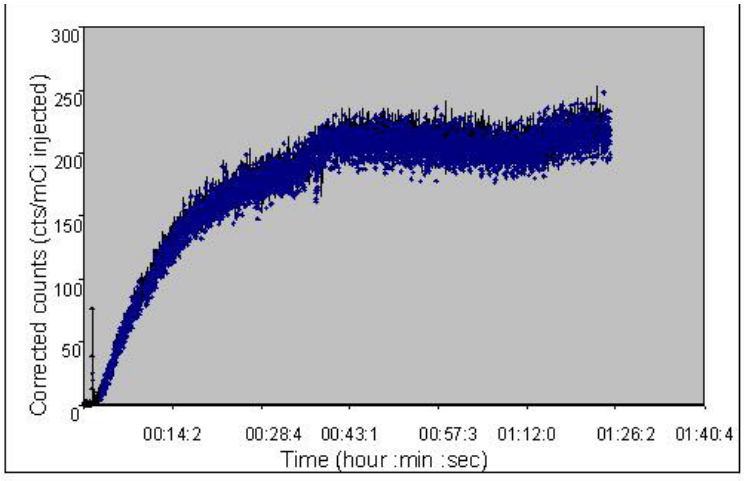
Methods: For biological applications, dendrimers and especially the so-called "dendron" building blocks are very promising as the diversity of functionalization brought by the arborescent structure simultaneously solves the problems of biocompatibility, low toxicity, large in vivo stability and specificity. Moreover, in addition to the multifunctionalization of a low molecular weight molecule, the arborescent monodisperse building blocks allow a versatility of size (according to the generation) and of physicochemical properties (hydrophilic, lipophilic). In the field of tree-like molecules, our work is focused on the development of a new dendro-chelate based on a synthetical water soluble siderophore (a tripodal derivative bearing one bidentate ligand on each arm) able to complex radioactive metals such as ^{99m}Tc(III). The arborescent PEGylated structure grafted at the focal point of the chelate is polyfunctional as the groups grafted at its periphery are either body- (or receptor-) specific, or allow the product to get through the BBB.

Results: A new dendritic ^{99m}technetium chelate 1 derived from a tripodal tris-catecholamide has been evaluated by in vitro toxicity measurements, radiolabelling ability (radiochemical yield and purity), kinetic stability and in vivo experiments as a Single Photon Emission Computed Tomography (SPECT) radiopharmaceutical. Also, a comparison with its corresponding diethylenetriamine pentaacetic acid (DTPA) homologue 2 allowed to assess the real impact of the pre-organized tripodal structure on the kinetic inertness (and thus toxicity), which is an important issue to address when considering in vivo applications.

Conclusions: Radiolabelling was performed using the stannous chloride reduction method: while DTPA-homologue 2 showed a high radiolabelling efficiency (96% radiolabelling yield after 30 minutes), tripodal complex 1 induced a 93% complexation rate after 1h30 minutes. In contrast, radiocomplex 1 derived from the most rigid and organized structure developed a kinetic stability by far more important than 2: indeed, while dissociation of 2 reached 50% after 1h30min in physiological media like phosphate buffer saline (PBS) and bovine serum albumin (BSA), over 80% of 1 remained stable during the half-life of the radionucleide (6,02 hours for ^{99m}Tc).



Stability as a function of time of radiolabelled complexes 1and 2 measured in buffer PBS (pH 7.4); error bars of 5%.



Cerebral kinetic (temporal counting statistics) of radiocomplex **1** followed by γ-camera at the central part of the mouse brain

SYNTHESIS AND EVALUATION OF N-(4-[11C]METHOXYPHENETHYL)ARACHIDONYLAMIDE AS PET RADIOLIGAND FOR IN VIVO IMAGING OF FATTY ACID AMIDE HYDROLASE IN THE BRAIN

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Objectives: Fatty acid amide hydrolase (FAAH) is one of the main enzymes responsible for terminating the signalling of endocannabinoids, including anandamide (AEA). Accumulating data suggest a link between FAAH and several neuronal and neuropsychiatric disorders. At present, no radioligand is available for mapping the enzyme in vivo. We have synthesized and evaluated a phenolic AEA analogue, N-(4-[^{11}C]methoxyphenethyl)arachidonylamide (^{11}C-1), as potential metabolic trapping tracer for in vivo study of brain FAAH.

Methods: 'Cold' compound 1 and desmethyl-1 were synthesized in a 2 step reaction starting from arachidonic acid. Binding of 1 (10μM) to hCB_1 and hCB_2 cannabinoid receptors was evaluated in a competition study with [^{3}H]-SR141716A (1nM) and [^{3}H]-CP55,940 (1nM). Interaction of 1 (10μM) with recombinant FAAH was evaluated by its ability to prevent the enzyme from hydrolysing [^{3}H]-AEA (2μM). Synthesis of ^{11}C-1 was done by heating 3 μmol desmethyl-1 with $^{11}CH_3I$ in 240 μl DMF at 50°C for 10 min in the presence of 10 μl NaH. ^{11}C-1 was purified by RP-HPLC and concentrated on a C_{18} seppak. Biodistribution of ^{11}C-1 was studied in wild type (WT) and FAAH knock-out (KO) mice after i.v injection of 3.7MBq ^{11}C-1. At 1, 10 and 30 min (n=3) post injection (18 - 37 MBq of ^{11}C-1), metabolite analysis in WT and KO mice was performed. Plasma and brain proteins were precipitated with CH_3CN and supernatant was analyzed by RP-HPLC.

Results: 1 displayed in vitro interaction with FAAH as it is substrate of the enzyme. 1did not displayed significant binding to hCB_1 and hCB_2 receptors, a condition to be useful as FAAH tracer. Based on $^{11}CH_3I$, ^{11}C-1 was obtained in a decay-corrected RCY of 28 % with a radiochemical purity of > 98 % and specific activity of 60 – 100 GBq/μmol. ^{11}C-1 demonstrated brain uptake (0.841% ± 0.087 ID/g at 1 min in WT and 0.545% ± 0.123 ID/g at 1min in KO mice) with high blood activity at all time points. Brain uptake in KO mice was statistically different from brain uptake in WT mice at all time points. Metabolite studies showed rapid metabolisation of ^{11}C-1 both in blood (69.3, 7.9, 7.9% intact product at 1, 10, 30 min p.i. respectively) and brain (77.7, 9.9, 6.5% at 1, 10, 30 min p.i. respectively) in WT mice. As expected, slower metabolisation was detected in KO mice in blood (89.1, 36.3, 17.7% intact product at 1, 10, 30 min p.i. respectively) and brain (80.9, 55.1, 31.0% intact product at 1, 10, 30 min p.i. respectively). Metabolisation in blood in KO mice was statistically different from metabolisation in WT mice at 10 min p.i.. For the brain, metabolisation was statistically different from metabolisation in WT mice at 10 and 30 min p.i.

Conclusions: 1 interacts with FAAH as a substrate and displays no significant binding to hCB_1 and hCB_2 cannabinoid receptors. We have successfully labelled it with ^{11}C and demonstrated its brain uptake. The metabolite profile should be further evaluated. Together these data suggest that 1 can serve as an entry point to the preparation of FAAH imaging agents.

IN VITRO AND IN VIVO CHARACTERIZATION OF [F-18]MK-1312: A PET TRACER FOR QUANTIFICATION OF MGLUR1 RECEPTOR OCCUPANCY BY MK-5435

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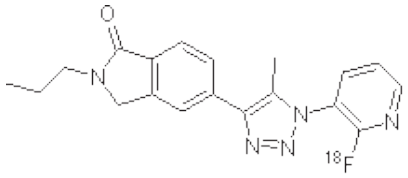
Objectives: Metabotropic glutamate receptor subtype 1 (mGluR1) has been suggested to play an important role in neurological processes, and mGluR1 allosteric antagonists have been proposed as therapeutic agents for the treatment of various psychiatric diseases. We sought to discover an mGluR1 selective PET tracer for quantifying receptor occupancy (RO) in preclinical and clinical studies with mGluR1 allosteric antagonist MK-5435.

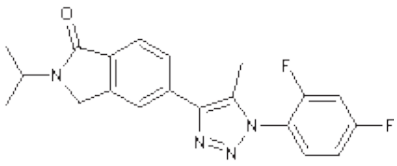
Methods: [^{18}F]MK-1312 was synthesized with high specific activity (average = 2175 Ci/mmol, n = 22) by microwave-assisted nucleophilic displacement of a 2-chloropyridine precursor with [^{18}F]KF/K222. In vitro autoradiography was performed on coronal brain sections incubated with [^{18}F]MK-1312 at rt with or without 10 μM MK-5435. In vitro saturation binding studies were performed using cerebellum homogenates. In vivo PET studies were carried out on fasted rhesus monkeys anesthetized with propofol. MK-5435 was administered IV as a bolus plus infusion to achieve steady-state drug plasma levels throughout the PET scan. [^{18}F]MK-1312 was administered as an IV bolus one hour post MK-5435 infusion. Blood samples were collected for determination of MK-5435 plasma levels. Regions of interest were drawn on summed PET images and projected onto the dynamic scans to obtain the time-activity curve (TAC). TACs were expressed in Standard Uptake Value (SUV) units (normalized with monkey body weight and tracer injected dose). MGluR1 receptor occupancy was determined for the cerebellum with the area-under-the-curve method using the 60-90 min time frame of the TACs. Free + nonspecific binding was estimated using the TAC from the region of lowest uptake (striatum) at the highest dose of MK-5435 (near full-blockade).

Results: In vitro autoradiography with [^{18}F]MK-1312 in rhesus monkey and human brain slices showed an intense signal in the cerebellum, a moderate signal in thalamus and hippocampus, and the lowest signal in the cortical areas and striatum, similar to the reported mGluR1 distribution. Baseline PET scans with [^{18}F]MK-1312 in rhesus monkey showed tracer distribution consistent to that observed in vitro. Blockade of [^{18}F]MK-1312 uptake by pre-administration of MK-5435 was found to be dose-dependent. The relationship between MK-5435 plasma concentration and PET determined RO fit a sigmoidal curve with a Hill coefficient of 0.84, and 75% receptor occupancy is achieved at 280 nM. Binding studies in cerebellum homogenates indicated a similarly high Bmax/Kd ratio of 132 and 98 for rhesus monkey and human, respectively. This suggests that a specific signal of useful magnitude may be obtained in human PET studies.

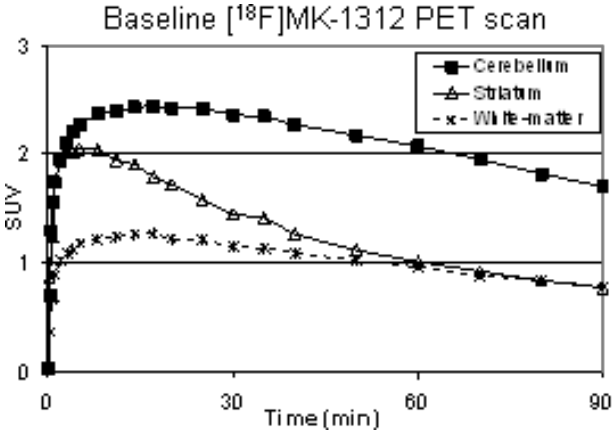
Conclusions: Preclinical studies have demonstrated that [^{18}F]MK-1312 is a useful tool for determining the relationship of mGluR1 occupancy by MK-5435 to its steady-state plasma levels in non-human primates, and may be useful for MK-5435 dose selection in clinical studies.

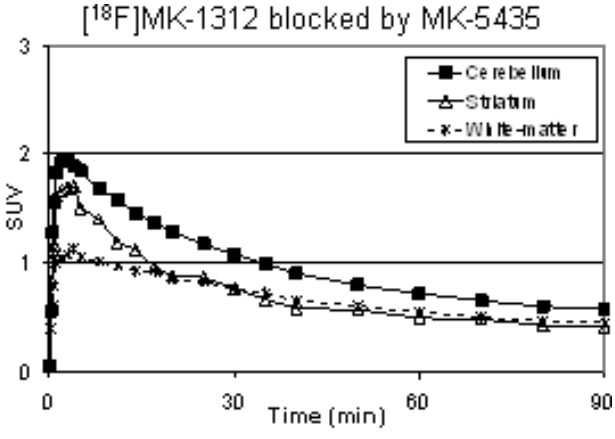


[^{18}F]MK-1312



MK-5435





SYNTHESIS AND PRELIMINARY EVALUATION OF [11C]JHU87728, A FLUOROPIPERIDINYL ANALOG OF THE CB1 RADIOLIGAND [11C]OMAR ([11C]JHU75528)

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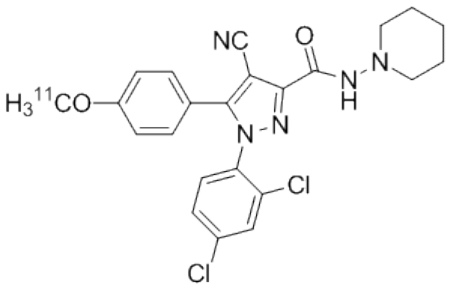
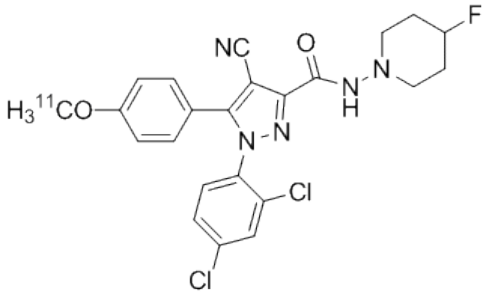
Objectives: Currently [^{11}C]OMAR ([^{11}C]JHU75528) is a radioligand of choice for PET imaging of cerebral CB1 receptors in animals and humans. Similar to its analog Rimonabant, [^{11}C]OMAR undergoes hepatic metabolism that is likely to involve hydroxylation of N-aminopiperidine ring. In order to obtain a CB1 radioligand with reduced rate of oxidative metabolism and, potentially, greater brain uptake we synthesized [^{11}C]JHU87728, a fluoropiperidinyl analog of [^{11}C]OMAR. Initial in vitro and in vivo evaluation of [^{11}C] JHU87728 is presented.

Methods: JHU87728 (4-cyano-1-(2,4-dichlorophenyl)-N-(4-fluoropiperidin-1-yl)-5-(4-methoxyphenyl)-1H-pyrazole-3-carboxamide) was synthesized and its CB1 binding affinity was determined by inhibition binding assay. [^{11}C]JHU87728 (4-cyano-1-(2,4-dichlorophenyl)-N-(4-fluoropiperidin-1-yl)-5-(4-[^{11}C]methoxyphenyl)-1H-pyrazole-3-carboxamide) was prepared by radiomethylation of the corresponding phenol precursor with [^{11}C]methyl triflate. [^{11}C]JHU87728 was injected in baboon and its brain distribution was studied by HRRT PET imaging. Metabolism of [^{11}C]JHU87728 in baboon plasma was determined by HPLC analysis.

Results: JHU87728 displayed a binding affinity value of 23 and 52 nM. [^{11}C] JHU87728 was prepared with an average radiochemical yield of 20%, radiochemical purity greater than 95% and specific activity of 7000 mCi/mmol at the end-of-synthesis. Analysis of baboon plasma showed a slightly reduced rate of metabolism of [^{11}C] JHU87728 compared to its lead analog [^{11}C]OMAR. In baboon brain [^{11}C] JHU87728 exhibited a regional distribution that was consistent with distribution of CB1 receptors. The putamen/thalamus ratio value (1.9 at 82 min post injection) of [^{11}C] JHU87728 was lower than that of [^{11}C]OMAR (2.3-2.5) that is consistent with lower binding affinity of the new radioligand whereas the total brain uptake of both radioligands was comparable.



[^{11}C]OMAR ([^{11}C]JHU75528)



[^{11}C]JHU87728

Research Support: This work was supported in part by NIH/NIMH grant MH-079017 (AGH)

SYNTHESIS AND MICROPET EVALUATION OF THE RADIOLABELLED P-GLYCOPROTEIN INHIBITOR [11C]ELACRIDAR

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Objectives: The efflux transporter P-glycoprotein (P-gp), which is highly expressed in the blood-brain barrier (BBB), protects the brain from xenobiotics. Changes in P-gp expression and function are thought to be implicated in several neurologic disorders such as epilepsy, Alzheimer's and Parkinson disease. Radiolabelled P-gp substrates, such as [^{11}C]verapamil and [^{11}C]loperamide, have been used to visualize cerebral P-gp function with PET, but possess very low brain uptake. Radiolabelled inhibitors of P-gp, which bind to P-gp without being transported, might possess higher brain uptake and afford signal increases in brain regions that overexpress P-gp. The aim of this work was to synthesize and evaluate the radiolabelled third-generation P-gp inhibitor [^{11}C]elacridar in μPET experiments.

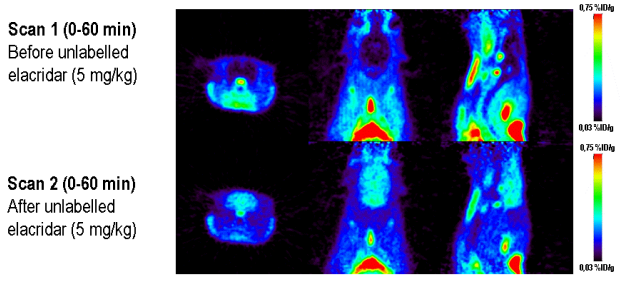
Methods: An elacridar analogue bearing a phenolic hydroxyl function in the acridone moiety was synthesized in 5 steps starting from 5-methoxyacridone-4-carboxylic acid. O-Desmethylelacridar was reacted with [^{11}C]methyl triflate in acetone (containing 3 eq. of aq. sodium hydroxide) to yield [^{11}C]elacridar, using a TRACERlab FX C Pro synthesis module coupled to a [^{11}C]CH_4 target (General Electric). Female Sprague-Dawley rats (n=3) underwent paired [^{11}C]elacridar μPET scans and arterial blood sampling. A baseline scan (140 min), during which unlabelled elacridar (5 mg/kg) was administered i.v. at 60 min after radiotracer injection, was followed by a second 60-min scan at 2h after administration of unlabelled elacridar.

Results: [^{11}C]Elacridar was synthesized in a decay-corrected radiochemical yield of 5±1% (n=14), based on [^{11}C]methyl triflate, with a specific activity >370 GBq/μmol. In baseline μPET experiments, brain uptake of radioactivity was rather low (0.05 %ID/g from 5-60 min after radiotracer injection). Injection of unlabelled elacridar at 60 min after [^{11}C]elacridar injection, resulted in pronounced influx of radioactivity into brain reaching about 700% of baseline values at 130 min after radiotracer injection. In the second μPET scan (2h after injection of unlabelled elacridar), radioactivity in brain was about 4-fold higher than in the baseline experiment.

Conclusions: Our data suggest that a tracer dose of [^{11}C]elacridar is captured by P-gp in the BBB. Radiotracer displacement by unlabelled elacridar appeared to result in a breakthrough of activity into brain parenchyma, thereby suggesting specific interaction of [^{11}C]elacridar with P-gp in the BBB. The usefulness of [^{11}C]elacridar for the visualization and quantification of cerebral P-gp merits further investigation.

Research Support: The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement number 201380 and from the Austrian Science Fund (FWF) project "Transmembrane Transporters in Health and Disease" (SFB F35).

Paired [^{11}C]elacridar microPET scan in rat



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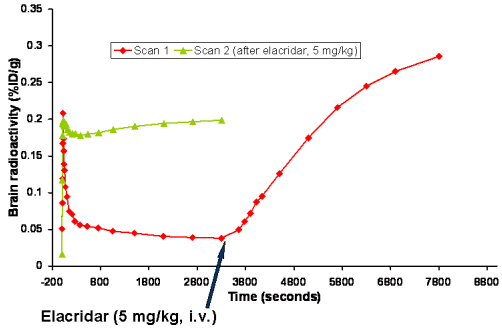
TACs of paired [^{11}C]elacridar microPET scan



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RADIOSYNTHESIS OF AN IMPROVED AMYLOID PROBE, [11C]AZD2184: PET CHARACTERIZATION IN THE CYNOMOLGUS MONKEY AND HUMAN BRAIN

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Objectives: Senile plaques consist of amyloid aggregates and imaging of these plaques using PET may be a route for early diagnostics of Alzheimer's disease (AD). The to date most extensively studied radioligand for this purpose is [^{11}C]PIB, however high levels of white matter retention limits its usefulness for detecting early and small loads of plaques. A high-resolution probe for imaging amyloid deposits, AZD2184 (5), has recently been described (Johnson et al. 2009). The objective of the present study was to label 5 with carbon-11, perform in vivo characterization in the cynomolgus monkey and human brain as well as analyzing the metabolism of the labeled probe.

Methods: Three different paths were employed to label [^{11}C]5 (Gravenfors et al. 2007, patent) (see figure). LC-MS-MS was used to ensure the identity of the labeled radioligand. Four PET measurements in two cynomolgus monkeys were performed with [^{11}C]5 and radiometabolites in monkey plasma were analyzed using HPLC. A preliminary clinical evaluation of the radioligand was also carried out in AD patients.

Results: Direct methylation using [^{11}C]MeOTf of 1 yielded no [^{11}C]4 or [^{11}C]5. Addition of aqueous base resulted in only O-methylation ([^{11}C]4). Adding the weak base TMP we were only able to observe a 2% yield of [^{11}C]5. Protecting the phenol made it possible to label the compound using [^{11}C]MeI and KOH in DMSO with an incorporation yield from [^{11}C]MeI >50%. The subsequent deprotection steps were in both cases quantitative. Due to easier deprotection conditions, precursor 3 was used for all productions for PET. The total synthesis time was 30-33 minutes with a specific radioactivity of 1643-3371 GBq/umol at EOS and the radiochemical purity was >99%. The distribution of brain radioactivity was fairly uniform, with early to late brain concentration ratios (peak vs 60 min.) significantly higher for [^{11}C]5 than what has previously been reported for [^{11}C]PIB (Mathis et al. 2003) (8.2 and 4.6 respectively), indicating low levels of white matter retention. Metabolism of [^{11}C]5 was fast with less than 10% remaining in the plasma 15 minutes after administration. Summation images from AD patients clearly visualize high brain uptake of [^{11}C]5, mainly in cortical regions, while a homogenuos uptake and a fast washout was evident in young control subjects.

Conclusions: A successful 2-step labelling method of [^{11}C]AZD2184 was developed. [^{11}C]AZD2184 shows a pre-clinical and clinical profile that suggests an improved signal in PET compared to currently used radiotracers for the visualisation of amyloid plaques due to a low level of white matter retention.

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