P017 SYNTHESIS AND FLUORINE-18 LABELING OF 6-FLUORO-PBR28, A CANDIDATE FOR IMAGING THE PERIPHERAL BENZODIAZEPINE RECEPTOR WITH PET

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Objectives: The peripheral benzodiazepine receptor (or TSPO 18 kDa) is expressed by microglial cells in many neuropathologies involving neuroinflammation. [^{11}C]PK11195 is today the most widely used radioligand for the in vivo imaging of PBR using PET, and this in spite of its low brain uptake and its high level of non-specific binding. Numerous PK11195 challengers are currently under investigation [1], and of particular interest are the N-benzyl-N-(2-phenoxyaryl)-acetamides, a series which today includes [^{11}C]DAA1106, [^{18}F]FEDAA1106, but also [^{11}C]PBR28, a recently reported compound displaying exceptional in vivo binding properties and currently further evaluated in primates and humans [2-7]. PBR28 is a meta/para-bi-substituted pyridine, leaving open the option of fluorine introduction at an ortho position, and therefore offering an opportunity for labeling with the longer half-life positron-emitter fluorine-18 using the well-established nucleophilic ortho-heteroaromatic radiofluorination methodology [8]. A first analogue, 6-fluoro-PBR28 (N-(2-methoxybenzyl)-N-(6-fluoro-4-phenoxypyridinyl-3-yl)acetamide, (1)), was designed, synthesized and labeled with fluorine-18, which is the subject of the work presented herein.

Methods: 6-Fluoro-PBR28 (1), as well as the corresponding 6-chloro and 6-bromo derivatives (2a and 2b) were all synthesized from commercially available 4-chloro-3-nitropyridine. The common intermediate in our approach is 3-nitro-4-phenoxypyridin-6-ol, a tri-substituted pyridine that can be further reacted either with $POCl_3$, $POBr_3$ or DAST to provide the corresponding key 6-halogenopyridines. Labeling of 6-fluoro-PBR28 (1) with fluorine-18 involves the following steps: (A) reaction of K[^{18}F]F-Kryptofix®222 with 2-3 mg of precursor (2a or 2b) at 165°C for 5 min in DMSO, (B) PrepSep C-8 cartridge pre-purification, (C) purification using semi-preparative reversed-phase HPLC (Waters Symmetry® C-18 - eluent : ACN / H_2O / PicB7 : 35 / 65 / 2 (v/v/v) - flow rate : 5 mL/min - detection at 254 nm) and (D) SepPak®Plus-based formulation.

Results: 6-Fluoro-PBR28 and its chloro/bromo analogues were all synthesized in six chemical steps and obtained in 16%, 10% and 19% overall yield, respectively. Ready-to-inject 6-[^{18}F]fluoro-PBR28 (>95% radiochemically pure) was prepared within 90 minutes (including HPLC-purification, R_t : 23-24 min) using our Zymate-XP robotic system. Typically, starting from a 37 GBq cyclotron-produced [^{18}F]fluoride batch, 3.3-3.7 GBq of 6-[^{18}F]fluoro-PBR28 could be obtained starting from the bromo derivative (9-10% non-decay-corrected overall yield, non-optimized). Specific radioactivities ranged from 74-148 GBq/μmol. Comparable radiochemical yields were obtained using the chloro precursor for labeling with however a lower observed chemical purity (so far <70%).

Conclusions: 6-Fluoro-PBR28 (1) was labeled with fluorine-18 in one single step using a bromine-for-fluorine (or chlorine-for-fluorine) heteroaromatic substitution. Dynamic μPET studies are currently underway in our rodent model of neuroinflammation (unilaterally AMPA-induced striatum-lesioned rats).

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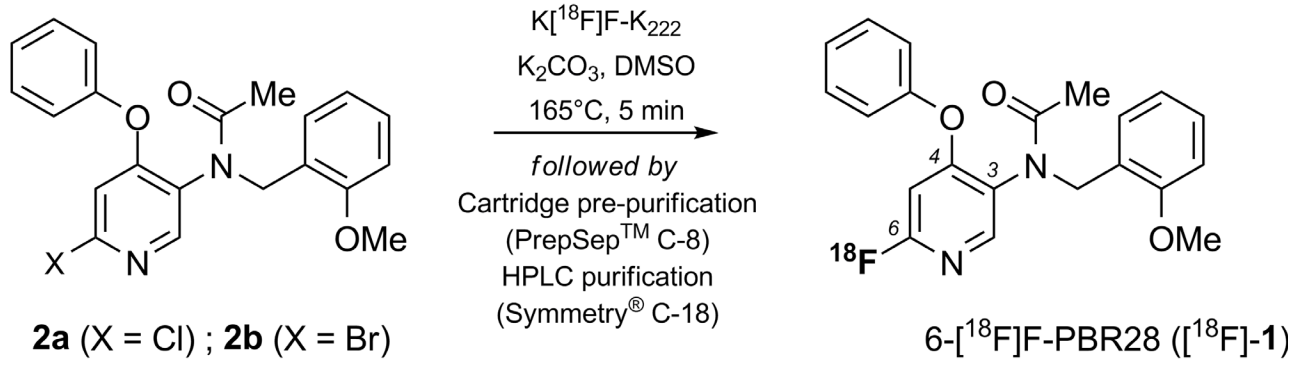
References: [1] Chauveau et al. Eur. J. Nucl. Med. Mol. Imag. (2008), 35, 2304-2319. [2] Briard et al. J. Label. Compds Radiopharm. (2005), 48, S71. [3] Imaizumi et al. Neuroscience Lett. (2007), 411, 200-205. [4] Brown et al. J. Nucl. Med. (2007), 48, 2072-2079. [5] Imaizumi et al. Neuroimage (2008), 39, 1289-1298. [6] Briard et al. J. Med. Chem. (2008), 51, 17-30. [7] Fujita et al. Neuroimage (2008), 40, 43-52. [8] Dolle Curr. Pharm. Design (2005), 11, 3221-3235.



P018 [18F]FB-IL2: A NOVEL PET TRACER FOR DETECTION OF ACTIVATED T-LYMPHOCYTES

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Objectives: Interleukin 2 (IL2) is a small single-chain glycoprotein (15.5 kDa) of 133 amino acids that is synthesized and secreted in vivo by activated T lymphocytes. IL2 binds with high affinity and specificity to the cell membrane IL2 receptor, which is overespressed on activated T lymphocytes in various pathological conditions.[1] ^{99m}Tc-labelled IL2 showed to be a good radiopharmaceutical with high diagnostic potential to detect activated T lymphocytes during the early stage of inflammatory and autoimmune diseases. Here, we report the synthesis of the new PET tracer [^{18}F]FB-IL2 by conjugation of N-succinimidyl 4-[^{18}F] fluorobenzoate ([^{18}F]SFB) to a lysine residue in the IL2 protein.

Methods: [^{18}F]SFB was synthesized in three steps by slight modification of the procedure described by Wester et al.[2] The synthesis was fully remote-controlled using a Zymark robotic system. Conjugation of [^{18}F]SFB to IL2 was performed in borate buffer pH 8.3 / ethanol (1/1). Reaction temperature (37–60 °C) and time of conjugation (5–30 min) were optimized. [^{18}F]FB-IL2 was purified by semi-preparative HPLC. The stability of [^{18}F]FB-IL2 in human plasma was tested in vitro by TCA precipitation. The integrity of [^{18}F]FB-IL2 was investigated by SDS-PAGE electrophoresis and the biological activity of the radiopharmaceutical was determined with an MTT proliferation assay using PHA-activated human lymphocytes.

Results: [^{18}F]SFB was reliably produced in 34–38% radiochemical yield. After SPE purification, the radiochemical purity of [^{18}F]SFB was 93–96%. The optimal reaction temperature for the conjugation of [^{18}F]SFB to IL2 was 50 °C. Higher temperatures caused degradation of the protein and hydrolysis of [^{18}F]SFB, whereas the reaction was substantially slower at lower temperatures. At 50 °C, the reaction was complete within 10 min. Under the optimized conditions, radiochemical yield of HPLC-purified [^{18}F] FB-IL2 was 25-35%. SDS-PAGE showed a single band for [^{18}F]FB-IL2 at the same height as that of native IL2, which indicates that no covalent aggregates of [^{18}F]FB-IL2 or degradation products were formed during labelling. The TCA precipitation assay showed that [^{18}F]FB-IL2 is quite stable in human plasma, as only 20% of soluble ^{18}F was released after 2h incubation at 37 °C. The MTT assay showed that [^{18}F]FB-IL2 stimulated lymphocyte proliferation to a similar extend as native IL2.

Conclusions: IL2 was successfully labelled with fluorine-18. [^{18}F]FB-IL2 is stable and its biological activity is retained during labelling and therefore could be a suitable new probe for PET imaging of activated T-lymphocytes. Animal PET imaging studies are currently in progress.

References: 1. Signore A et al., J Endocrinol Invest. 1999; 22:151-8. 2. Wester HJ et al., Nucl. Med. Biol. 1996; 23:365-372.

P019 SUITABILITY OF ENDOTHELIN RECEPTOR SUBTYPE A AS A TARGET FOR PET IMAGING OF ATHEROSCLEROTIC PLAQUES

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Objectives: Both subtypes of endothelin receptors (ET_A and ET_B) are regulators of vascular tone. While ET_B is associated with vasodilatation and vasoconstriction, ET_A mediates only vasoconstriction. ET_A is prevalently expressed on vascular smooth muscle cells of the human aorta and coronary arteries [1]. In atherosclerosis, an increased accumulation of smooth muscle cells in the atherosclerotic plaques can be found [2]. Consequently, an elevated number of ET_A should be detectable in the diseased area, which in turn might provide a suitable target for plaque imaging. In order to prove the suitability of ET_A for PET imaging of atherosclerosis, we examined the expression levels of ET_A on human atherosclerotic tissue samples using Western blotting. Furthermore, we developed a new selective ^{18}F-labelled ET_A antagonist for autoradiography studies and in vivo PET imaging. [1] C.R. Bacon et al., Br. J. Pharmacology 117 (1996), 986-992. [2] H.C. Stary et al., Circulation 92 (1995), 1355-1374.

Methods: The ^{18}F-labelled analogue of (E)-N-[6-(2-fluoroethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl) pyrimidin-4-yl]-2-phenylethensulfonamide [3] was radiofluorinated using n.c.a. [^{18}F]fluoride (Kryptofix 2.2.2/K_2CO_3) and the corresponding tosyl- as well as the bromide-precursor. Both precursors gave similarly good radiochemical yields of 20-30%. Samples of lesioned and healthy human artery were either homogenised for Western blotting or sectioned for autoradiography studies. Western blots were performed using polyclonal rabbit antibodies for both ET_A and ET_B. Autoradiography assay validation and preliminary tests were performed with the selective ET_A radioligand [^{3}H]BQ123. Non-specific binding was determined by co-incubation with endothelin-1 (ET-1). [3] H. Harada et al., Chem. Pharm. Bull. 49 (2001), 606-612.

Results: Two precursors for n.c.a. ^{18}F-fluorination of (E)-N-[6-(2-fluoroethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl) pyrimidin-4-yl]-2-phenylethensulfonamide were successfully synthesised and showed similar and good results in radiolabelling. Western blot analyses revealed lower levels of ET_A in diseased aorta compared to healthy tissue (relative to total protein). First autoradiography studies with [^{3}H]BQ123 showed low but specific binding to tissue slices without conclusive results on differences in receptor levels in healthy and diseased tissue.

Conclusions: Preliminary results from western blotting indicate for reduced levels of the ET_A in atherosclerosic plaques from human aorta. To clarify the applicability of the ET_A system for PET imaging of atherosclerosis, additional autoradiographical studies using the new ^{18}F-labelled selective ET_A antagonist and investigations on the mRNA levels of ET_A are in progress.

P020 [68Ga]FZ.MZ: A POTENTIAL IMAGING AGENT FOR ARTERIOSCLEOTIC PLAQUES

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Objectives: Cancer and atherosclerosis are highly relevant diseases and in the main focus of biomedical research. In this context, porphyrin derivatives are established biomolecules both in photodynamic therapy (PDT) and optical imaging[1] and also in atheromatous plaques via LDL endocytosis[3] are crucial physiological characteristics of these lipophilic compounds. As the generator-derived gallium-68 is a promising positron emitter for PET imaging, the complexation of this trivalent radiometal within tetrapyrrol ligands and their biological evaluation are reported in this study.

Methods: Benzyl-2-acetamido-3,6-di-O-acetyl-2,4-dideoxy-4-O-trifluoromethanesulfonyl-□-D-glucopyranoside) was synthesized from commercially available N-acetyl-glucosamine. The free hydroxyl groups on N-acetyl-glucosamine were acetylated and then the 4-acetyl group was selectively hydrolyzed by using a lipase enzyme. The resultant 4-hydroxy derivative was then treated with trifluoromethanesulfonic anhydride to give the triflate derivativewas then radioiodinated under both no-carrier added conditions and carrier-added conditions to yield the desired product.

Results: Elution of ^{68}Ga from the cationic exchange resin was achieved with only 600 μl of 98% acetone / 2% acaetylacetone. Three different porphyrin derivatives were labelled in yields ranging form 50 to 90% within 5 minutes using n.c.a. $^{68}Ga(acac)_3$ in chloroform. Radiochemical purities >95% were achieved by solid-phase extraction. Plasma incubation and DTPA challenge confirmed stability of the tracers over 2 hours. Due to their lipophilicity, ^{68}Ga-labelled prophyrins shows a LDL binding up to 50% and over 90% to HSA. Both have been identified as mechanisms for the uptake of porphyrins into artheromateous plaques. A preliminary μPET-study illustrates accumulation of the tracer in the tumor tissue.

Conclusions: Lipophilic porphyrin derivatives were rapidly labelled in high yields in a microwave-enhanced radiosynthesis. ^{68}Ga-labelling was achieved using solid-phase derived n.c.a $^{68}Ga(acac)_3$ as synthon under anhydrous conditions. The in vitro evaluations of these novel molecular imaging probes prove the potential for relevant medical application. Further investigation using PET are in progress.

References: 1. Pandey, S. K.; Gryshuk, A. L.; Sajjad, M.; Zheng, X.; Chen, Y.; Abouzeid, M. M.; Morgan, J.; Charamisinau, I.; Nabi, H. A.; Oseroff, A.; Pandey, R. K., Multimodality agents for tumor imaging (PET, fluorescence) and photodynamic therapy. A possible “see and treat” approach. J Med Chem 2005, 48, (20), 6286-95. 2. Juzeniene, A.; Peng, Q.; Moan, J., Milestones in the development of photodynamic therapy and fluorescence diagnosis. Photochem Photobiol Sci 2007, 6, (12), 1234-45. 3. Nakajima, S.; Takemura, T.; Sakata, I., Tumor-localizing activity of porphyrin and its affinity to LDL, transferrin. Cancer Lett 1995, 92, (1), 113-8. 4. Zhernosekov, K. P.; Filosofov, D. V.; Baum, R. P.; Aschoff, P.; Bihl, H.; Razbash, A. A.; Jahn, M.; Jennewein, M.; Rosch, F., Processing of generator-produced 68Ga for medical application. J Nucl Med 2007, 48, (10), 1741-8. 5. Zoller, F.; Riss, P.; Montsforts, F.; Rsch, F., Efficient radiosynthesis of lipophilic 68Ga-porphyrin complexes for multimodal molecular imaging Bioconj Chem 2009, submitted.

P021 A RADIOIODINATED LUMIRACOXIB DERIVATIVE: SYNTHESIS AND IN VITRO/IN VIVO EVALUATION AS A SPECT TRACER FOR CYCLOOXYGENASE-2 EXPRESSION

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Objectives: Although extensive investigations on the development of COX-2 imaging radiotracers have been conducted, currently no suitable PET/SPECT tracers are available for in vivo imaging of COX-2 expression. This study aims to synthesize and evaluate a radioiodinated derivative of lumiracoxib, 2-[(2-fluoro-6-iodophenyl)- amino]-5-methylphenylacetic acid (FIMA), which is structurally distinct from other drugs in the class and has weakly acidic properties, as a SPECT tracer for imaging COX-2 expression.

Methods: The radiosynthesis of ^{125}I- FIMA was performed with an electrophilic iododestannylation reaction. The COX inhibitory potency was assessed by measuring COX-catalyzed oxidation by hydrogen peroxide. Cell uptake characteristics of ^{125}I-FIMA were assessed in control and LPS/ IFN-γ-stimulated macrophages. The biodistribution of ^{125}I-FIMA was determined by the ex vivo tissue counting method in rats (n=5/group) at 10, 30, 60, and 180 min after the tracer injection. Accumulation of ^{125}I-FIMA in inflammatory tissues was also examined in rats with ear edema (n=4-5/group) at the same time points.

Results: ^{125}I- FIMA was obtained with the radiochemical yields of 38%, and the radiochemical purities of greater than 95%. The COX-2 inhibitory potency of FIMA (IC_{50} =2.46 μM) was higher than that of indomethacin (IC_{50} =20.9 μM) and comparable to those of lumiracoxib (IC_{50} =0.77 μM) and diclofenac (IC_{50} =0.98 μM). The IC_{50} ratio (COX-1/COX-2=182) indicated the high isoform selectivity of FIMA for COX-2. ^{125}I-FIMA showed 3.2-fold higher accumulation in COX-2 induced macrophages than in control macrophages, which was decreased by nonradioactive FIMA in a concentration dependent manner. The biodistribution study showed rapid clearance of ^{125}I-FIMA from the blood and most organs including the liver and kidneys. ^{125}I-FIMA showed no marked accumulation in the stomach (≤ 2.64 %ID) and thyroids (≤ 0.03%ID), indicating that radioiodinated FIMA was stable for in vivo deiodination. The radioactivity levels in the ear edema were significantly higher than those in the contra-lateral ears and the accumulation ratio of ear edema to normal ear was 1.4 at 180 min after the tracer injection.

Conclusions: FIMA showed a high inhibitory potency and selectivity for COX-2. Radioiodinated FIMA showed specific accumulation into COX-2 induced macrophages, and showed significantly higher accumulation in inflammatory ear edema than in contra-lateral ears. Thus, radioiodinated FIMA can be a potential candidate as a SPECT tracer for COX-2 expression.

P022 [18F]DPA-714, [18F]PBR111 AND [18F]FEDAA1106 AS POTENT PBR PET-IMAGING CANDIDATES: RADIOSYNTHESIS AND COMPARATIVE STUDIES

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Objectives: The 3-isoquinolinecarboxamide [^{11}C]PK11195, in spite of its low brain uptake and its high level of non-specific binding, is still today the most widely used PET-radioligand for the in vivo imaging of peripheral benzodiazepine receptor (PBR or TSPO 18 kDa). Numerous PK11195 challengers are currently under investigation [1], and of particular interest are DPA-714, PBR111 and FEDAA1106, three ligands belonging to different chemical classes (the pyrazolo[1,5-a]pyrimidineacetamides, the imidazo[1,2-a]pyridineacetamides and the N-benzyl-N-(2-phenoxyaryl)-acetamides, respectively) and labelled with the longer half-life positron-emitter fluorine-18. The present paper summarizes the radiosynthesis of these three compounds and presents the preliminary results of a comparative pharmacological evaluation by autoradiography in a rodent model of acute neuroinflammation (by unilateral AMPA injection in the striatum).

Methods: Fluorine-18 labelling of DPA-714, PBR111 and FEDAA1106 has been fully automated on our Zymate-XP robotic system and involves: (A) reaction of K[^{18}F]F-Kryptofix®222 with the appropriate tosyloxy precursor (10-12 μmoles) at 165°C for 5 min in DMSO (0.6 mL) followed by (B) PrepSep C-18 cartridge pre-purification, (C) semi-preparative HPLC purification on a Waters X-Terra™ RP18 or Waters Symmetry® C-18 and (4) SepPak®Plus-based formulation for i.v. injection. In vitro binding properties of these fluorine-18-labelled ligands were studied in a rat model of focal acute neuroinflammation, and were compared with the reference compound [^{11}C]PK11195, using autoradiography. An immunohistochemistry study was performed to validate the in vitro data.

Results: Typically, 5-7 GBq of [^{18}F]DPA-714, [^{18}F]PBR111 and [^{18}F]FEDAA1106 (> 95% chemically and radiochemically pure) could be obtained with specific radioactivities ranging from 37 to 111 GBq/μmol within 90 minutes (HPLC purification and SepPak®Plus-based formulation included), starting from a 37 GBq [^{18}F]fluoride batch. Radiotracer localisation as detected by autoradiography correlated well with expression of PBR by activated microglial cells as demonstrated by immunohistochemistry.

Conclusions: [^{18}F]DPA-714, [^{18}F]PBR111 and [^{18}F]FEDAA1106 were all synthesized using a simple one-step process (a tosyloxy-for-fluorine nucleophilic aliphatic substitution) in 8%-20% non decay-corrected and isolated radiochemical yield. Comparative PET-imaging (Focus 220 Concorde) including control kinetics and displacement studies with PK11195 and non-labelled ligands are currently underway. Data will be compared to that obtained with the reference compound [^{11}C]PK11195 in the same model.

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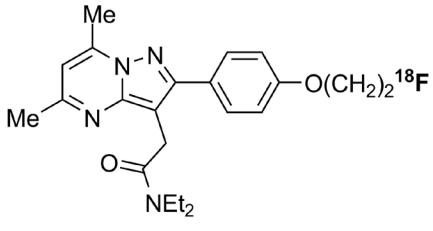
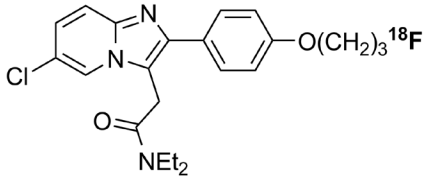
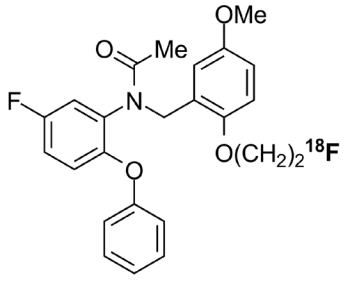
References: [1] Chauveau et al. Eur. J. Nucl. Med. Mol. Imag. (2008), 35, 2304-2319.



[^{18}F]DPA-714



[^{18}F]PBR111



[^{18}F]FEDAA1106

P023 SYNTHESIS AND EVALUATION OF [11C]DAC AS A NOVEL PERIPHERAL-TYPE BENZODIAZEPINE RECEPTOR PET LIGAND IN KAINIC ACID-LESIONED RAT

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Objectives: The peripheral-type benzodiazepine receptor (PBR, TSPO), which is an 18-kDa protein as a critical functional unit of a multimeric 140-200-kDa complex, is mainly distributed in the outer mitochondrial membrane at the cellular level. The PBR density was increased in the injured brain, and this increase has been used as an indicator of neuronal damage and several neurodenerative disorders such as Alzheimer's disease. We have previously developed three PET ligands [^{11}C]DAA1106[1], [^{18}F]FEDAA1106[2] and [^{11}C]AC-5216[3] for PBR imaging in the human brain. Here, we report radiosynthesis and evaluation of [^{11}C]DAC (N-benzyl-N-[^{11}C]methyl-2-(7,8-dihydro-7-methyl-8-oxo-2-phenyl-9H-purin-9-yl)acetamide) as a novel ligand for the PBR imaging. DAC is a novel compound with an oxopurine structure and has one less methyl group than AC-5216. DAC shows a slightly higher affinity for PBR (Ki: 0.23 nM) than PK11195 (0.31 nM). It also exhibits negligible activity for the other main receptors including central benzodiazepine receptor.

Methods: Radiolabeling was performed by reaction of a precursor with [^{11}C]CH_3I and NaOH in DMF. Biodistribution of [^{11}C]DAC was examined in normal mice and kainic acid (KA)-infused rat brains using the dissection method, autoradiogyaphy and small animal PET.

Results: Purification for the reaction mixture by a reversed-phase HPLC led to [^{11}C]DAC with >98% radiochemical purity. The total synthesis time was 21 min from EOB and the specific activity of [^{11}C]DAC in isotonic saline was determined to be 120 GBq/mmol (n=20) at EOS. The radiochemical purity of [^{11}C]DAC remained >95% after maintenance of the preparation at 25°C for 3 h, and it was stable for the time of a PET scan. After intravenous injection of [^{11}C]DAC into mice, high accumulation of radioactivity was found in the lung, heart, kidney and other PBR-rich regions. Metabolite analysis for the brain homogenate of mice determined that [^{11}C]DAC was in vivo stable. In vitro autoradiography for the KA-infused rat brain revealed that the total binding of [^{11}C]DAC increased 1.8-fold in the lesioned striatum, compared to the non-lesioned side. Treatment with unlabeled DAC and PK11195 completely blocked the increased binding in the lesioned striatum. PET experiments for KA-lesioned rats showed that the in vivo binding of [^{11}C]DAC to PBR was increased largely in the lesioned striatum, and [^{11}C]DAC showed a good contrast between the lesioned and non-lesioned striatum (the maximum ratio was about 3-fold). In displacement experiments, the uptake of [^{11}C]DAC in the lesioned striatum was blocked using an excess of either unlabeled DAC or PK11195 injected. These results demonstrated that [^{11}C]DAC had high in vivo specific binding to PBR in the injured rat brain.

Conclusions: [^{11}C]DAC is a useful PET ligand for PBR imaging and its specific binding to PBR is suitable as a new biomarker for brain injury.

References: 1) Zhang M.-R., Kida T., Noguchi J., et al. Nucl. Med. Biol. 30, 513-519 (2003). 2). Zhang M.-R., Maeda J., Ogawa M., et al. J. Med. Chem. 47, 2228-2235 (2004). 3) Zhang M.-R., Kumata K., Maeda J., et al. J. Nucl. Med. 48, 1853-1861 (2007).

P024 SYNTHESIS AND EVALUATION OF [18F]FEAC AND [18F]FEDAC AS TWO NOVEL POSITRON EMISSION TOMOGRAPHY LIGANDS FOR PERIPHERAL-TYPE BENZODIAZEPINE RECEPTOR IN THE BRAIN

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Objectives: In the central nervous system, peripheral-type benzodiazepine receptor (PBR, TSPO) is mainly located in glial cells, and PBR density was increased in glial cells activated by brain injury and neuroinflammation. Many studies have documented the relationship between PBR and brain injury or neuroinflammation in experimental animals and in human neurodegenerative diseases, such as Alzheimer's disease, stroke-induced brain injury etc. To characterize PBR in human brain, we have previously developed three PET ligands [^{11}C]DAA1106, [^{18}F]FEDAA1106 and [^{11}C]AC-5216 for PBR imaging. Here, using [^{11}C]AC-5216 as a lead compound, we designed two novel fluorinated ligands: [^{18}F]FEAC ([^{18}F]1) and [^{18}F]FEDAC ([^{18}F]2). These ligands were synthesized and evaluated as two putative PET ligands for PBR imaging.

Methods: [^{18}F]1 and [^{18}F]2 were synthesized by reacting their corresponding precursors with [^{18}F]FCH_2CH_2Br in the presence of NaOH at 90°C for 15 min, respectively. Biodistribution of [^{18}F]1 and [^{18}F]2 was examined in normal mice and kainic acid (KA)-infused rat brains using the dissection method, autoradiogyaphy and small animal PET.

Results: Purification for the reaction mixtures using reversed phase semi-preparative HPLC gave [^{18}F]1 and [^{18}F]2 in 35% and 46% (n=4) radiochemical yields based on the total [^{18}F]F, corrected for physical decay in a synthesis time of 45±2 min from the end of bombardment, respectively. In the final product solutions, the radiochemical purity of [^{18}F]1 and [^{18}F]2 was higher than 98% and their specific activity was 70–130 GBq/mmol. Moreover, their radiochemical purity remained >95% after 180 min at 25°C, and these radioligands were stable for the time of a PET scan. In vitro binding assay determined that the novel compounds 1 and 2 had high affinity and selectivity for PBR. In vivo uptake (SUV) and kinetics of [^{18}F]1 and [^{18}F]2 in neuroinflammatory rat brains was examined using a small-animal PET scanner. The two ligands entered the brain rapidly and the radioactivity level peaked within 1–3 min after injection. Higher uptake of these ligands was determined in the lesioned striatum than in the non-lesioned striatum. [^{18}F]1 and [^{18}F]2 showed relatively rapid clearance from the two sides. The maximum SUV in the lesioned and non-lesioned striatum was about 1.2 and 0.8 ([^{18}F]1), 1.8 and 0.9 ([^{18}F]2), respectively. [^{18}F]1 and [^{18}F]2 displayed the maximum ratio (2.5–3.0) of radioactivity between the two sides within 10–20 min.

Conclusions: [^{18}F]FEAC ([^{18}F]1) and [^{18}F]FEDAC ([^{18}F]2) are promising PET ligands for PBR imaging and could be useful in detecting tiny changes in PBR expression.