DEVELOPMENT OF A PET RADIOLIGAND FOR THE 5-HT1B RECEPTOR FROM A COMPOUND LIBRARY: RADIOSYNTHESIS, CHARACTERIZATION IN THE PRIMATE BRAIN AND METABOLITE ANALYSIS

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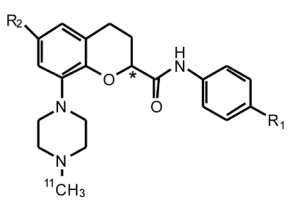
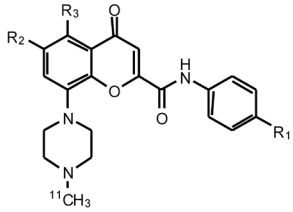
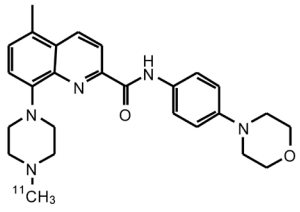
Objectives: The serotonin 1B receptor (5-HT_{1B}) has been implicated in several psychiatric disorders and is a potential pharmacological target in the treatment of depression. The aim of this study was to develop a radioligand for PET imaging of the 5-HT_{1B} receptor in human subjects in vivo. AR-A000002 has previously been shown to be a selective 5-HT_{1B} antagonist (Ahlgren et al. 2004), with a chemical structure deemed reasonable as a starting point for the series of compounds in this study.

Methods: Eight potential radioligands were identified (see figure) from a compound library, and are analogues of the reference 5-HT_{1B} antagonist AR-A000002. These selected compounds shared characteristics such as high affinity (0.1 – 0.5 nM), at least a 10 fold selectivity for the 5-HT_{1B} receptor, moderate lipophilicity with LogD around 1.5, and were not blood brain barrier efflux substrates. The compounds were radiolabeled with carbon-11 employing N-methylation using [^{11}C]methyl triflate on the piperazine structural moiety and purification using reversed phase HPLC. In vivo evaluation of each radioligand was performed using PET in cynomolgus monkey, as well as analysis of radioactive metabolites in plasma using HPLC.

Results: The eight compounds were labelled with carbon-11 in a total synthesis time of less than 35 minutes. Incorporation yields from [^{11}C]methyl triflate was >60% for all productions. The mean specific radioactivity was 290 GBq/umol (n = 14) at EOS. Initial in vivo PET measurements in cynomolgus monkey showed that six of the radiolabeled compounds had potential as radioligands, showing high brain uptake (3-4% ID) with a heterogenous distribution following the known density of 5-HT_{1B} receptors and low binding in cerebellum. Compound 1-4, 6 and 8 entered the brain successfully whereas compound 5 and 7 are less lipophilic than the other radioligands and showed low brain uptake. Compound 1 and 8 showed relatively high non specific binding, and had higher lipophilicity. The racemate 2 and the separated enantiomers 3 and 4, showed relatively higher binding in cerebellum resulting in lower specific binding ratio when compared to compound 6. Compound 1-4 showed faster metabolism with 15-50% of radioactivity representing unchanged radioligand 30 minutes after administration whereas 50-80% was unchanged for compound 5-8 at 30 minutes after administration.







8.

	R_1	R_2	*
1.		F	Racemate
2.		H	Racemate
3.		H	R
4.		H	S

	R_1	R_2	R_3
5.		F	H
6.		H	CH_3
7.		H	H

Conclusions: Compound 6 was the most promising radioligand of eight tested candidates and was nominated for further pre-clinical characterization and PET-examination in human subjects. Liphophilicity was a physiochemical property showing relation to favorable characteristics for in vivo imaging. The development program lead to identification of the first successfull PET radioligand for visualization of 5-HT_{1B} receptors in the human brain (Pierson et al. 2008).

References: Ahlgren, C., Eriksson, A., Tellefors, P., Ross, S.B., Stenfors, C., Malmberg, A., Eur J Pharmacol. 499(1-2), 67-75, 2004. Pierson, M.E., Andersson, J., Nyberg, S., McCarthy, D.J., Finnema, S.J., Varnas, K., Takano, A., Karlsson, P., Gulyas, B., Medd, A.M., Lee, C.M., Powell, M.E., Heys, J.R., Potts, W., Seneca, N., Mrzljak, L., Farde, L., Halldin, C., Neuroimage. 41(3), 1075-85, 2008..

COMPARISON OF DOPAMINE RECEPTOR BINDING OF FALLYPRIDE AND NORFALLYPRIDE

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Objectives: Dopamine D2 and D3 receptors are involved in several neurological and psychiatric disorders. ^{18}F-Fallypride is used to image both D2 and D3 receptor subtypes because of its high affinity for both receptor subtypes. There is greater interest in evaluating these receptor subtypes separately and efforts are underway in our laboratories to develop agonists and antagonists for the two subtypes. In efforts to develop antagonists, we have altered the structure of fallypride. A 2 to 3 carbon chain (ethyl, propyl, allyl) is considered an optimal substituent at the pyrrolidine nitrogen of fallypride for receptor binding. In order to evaluate effects of removal of the allyl group in fallypride, we have developed ^{18}F-Norfallypride ((S)-N-[(2-pyrolidinyl)methyl]-2,3-dimethoxy-5-(3'-flouropropyl)benzamide). We report synthesis and comparison of binding of ^{18}F-norfallypride with ^{18}F-fallypride.

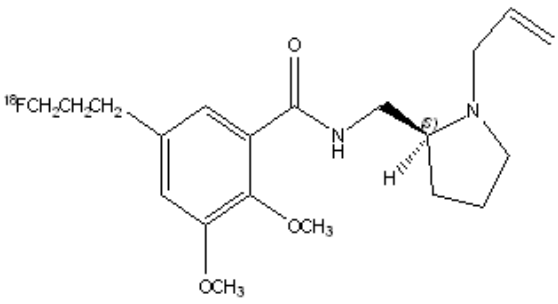
Methods: ^{18}F-Fallypride was synthesized using previously reported procedures (Mukherjee et al., 1995). Norfallypride was synthesized using (S)-1-BOC-2-(aminomethyl)pyrrolidine and 2,3-dimethoxy-5-(3'-flouropropyl)benzoic acid, followed by acid deprotection of the BOC group. Tosylate ((S)-N-[(1-BOC-2-pyrolidinyl)methyl]-2,3-dimethoxy-5-(3'-tosyloxypropyl)benzamide) was radiolabeled with ^{18}F-Kryptofix-K_2CO_3 in CH_3CN at 96 °C for 30 min and deprotected with trifluoroacetic acid (10% in CH_2Cl_2) at 80 °C to yield ^{18}F-norfallypride. In vitro binding on 10 μm brain slices were carried out. Rat MicroPET imaging in rats (after 0.8-1 mCi iv) was carried out followed by ex vivo autoradiographic analysis on 40 μm brain slices.

Results: ^{18}F-Norfallypride was made in modest yields (15%, decay uncorrected) in specific activities of >2Ci/μmol (60%CH_3CN-0.1%Et_3N in water, flow rate 2.5 ml/min-C18 semiprep; ret. time 21 min). Norfallypride displaced striatal ^{18}F-fallypride from brain slices with an affinity of 0.63 μM, suggesting weak binding to the D2 receptor. In vitro studies indicated selective binding to the striata (ST) (ratio of 4 ST/Cerebellum (Cb) for ^{18}F-norfallypride and 60 for ^{18}F-fallypride) both of which were displaced by 10μm sulpiride. Significant binding in the hippocampus was seen with ^{18}F-norfallypride compared to ^{18}F-fallypride. Very low brain uptake of ^{18}F-norfallypride was observed in the rat MicroPET study compared to ^{18}F-fallypride. Ex vivo scan of the brain revealed binding of ^{18}F-norfallypride to several regions; ex vivo micropet autoradiographic analyses of ^{18}F-norfallypride gave ratios with respect to Cb: ST=9 (60 for ^{18}F-fallypride); Nucleus accumbens (NA)=6; Hippocampus (HP)=6; Hypothalamus (HT)=9; Cerebellar Nuclei (CN)=7.

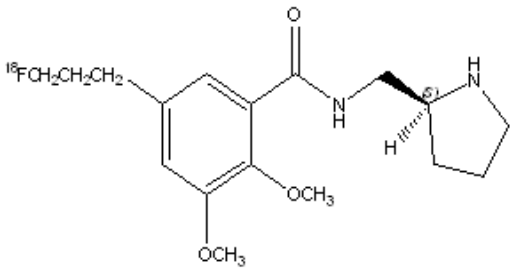
Conclusions: ^{18}F-Norfallypride binds uniquely to brain regions that are different from ^{18}F-fallypride and are likely to reflect distribution of the D3 receptor subtype. Studies to examine receptor subtype selectivity and increase brain uptake of ^{18}F-norfallypride are currently underway.

Research Support: NIH R01 EB006110

References: Mukherjee, J. et al., Nucl. Med. Biol., 22:283-296, 1995



^{18}F-Fallypride



^{18}F-Norfallypride

EFFECT OF FENFLURAMINE ON 5-HT1B BINDING OF [11C]AZ10419369 IN THE PRIMATE BRAIN

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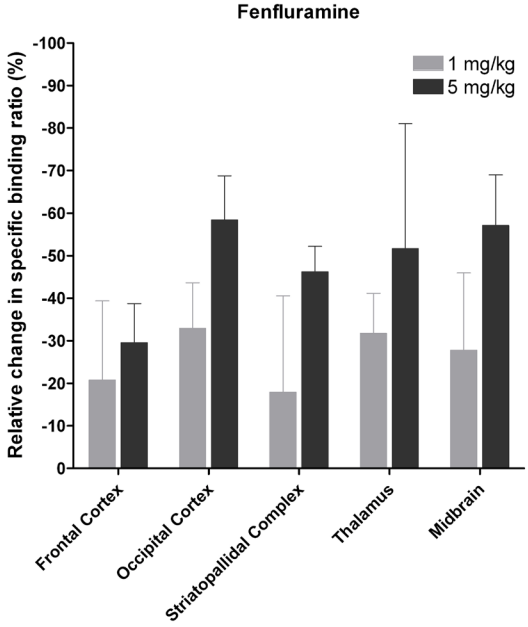
Objectives: Changes in endogenous neurotransmitter levels can be measured in the living brain using PET. Altered dopamine levels can, for instance, be evaluated with [^{11}C]raclopride. In contrast, the detection of modified serotonin levels has had more limited success. In a recent development program we evaluated eight compounds as candidate PET radioligands for the serotonin 5-HT$_{1B}$ receptor. The most suitable candidate found was the antagonist [^{11}C]AZ10419369, and we recently reported an initial PET-study using this selective radioligand (Pierson et al., 2008). The 5-HT$_{1B}$ receptor has a role in the modulation of synaptic serotonin release. The aim of the present study was to assess the sensitivity of [^{11}C]AZ10419369 binding to pharmacological manipulation of endogenous serotonin levels in cynomolgus monkeys.

Methods: A total of 12 PET measurements were conducted on six experimental days in three cynomolgus monkeys. On each day two measurements were performed using i.v. bolus administration of [^{11}C]AZ10419369. A baseline measurement was followed by a displacement measurement in which fenfluramine (1.0 or 5.0 mg/kg) was infused i.v. between 15 and 20 minutes after radioligand injection. The monkeys were anaesthetized with sevofluran (2-5%), except in two measurements where a mixture of ketamine and xylazine was used. Emission data were acquired for 123 minutes using the HRRT PET-system. The specific binding ratio was calculated as the ratio of the area under the curve (45-123 min) of the target region to the reference regions (cerebellum). The displacement effect was estimated as relative change (%) in specific binding ratio.

Results: Administration of fenfluramine had no evident effect on radioactivity in the reference region (cerebellum). After administration of fenfluramine (1.0 and 5.0 mg/kg), the respective binding ratios decreased in the occipital cortex by 33 ± 11% and 58 ± 10%, in striatopallidal complex by 18 ± 23% and 46 ± 6%, in thalamus by 32 ± 9% and 52 ± 29%, in frontal cortex by 21 ± 19% and 29 ± 9%, and in midbrain by 28 ± 18% and 57 ± 12%, respectively (Figure 1).

Conclusions: This preliminary study indicates for the first time the sensitivity of an antagonist 5-HT$_{1B}$-ligand to endogenous serotonin levels in vivo. [^{11}C]AZ10419369 may accordingly serve as a tool to further examine serotonin-related brain functions and psychiatric disorders, as well as effects of drugs on endogenous levels of serotonin in brain.

References: Pierson, M.E., Andersson, J., Nyberg, S., McCarthy, D.J., Finnema, S.J., Varnas, K., Takano, A., Karlsson, P., Gulyas, B., Medd, A.M., Lee, C.M., Powell, M.E., Heys, J.R., Potts, W., Seneca, N., Mrzljak, L., Farde, L., Halldin, C., Neuroimage. 41(3), 1075-85, 2008.



SYNTHESIS AND EVALUATION OF A C-11 LABELED DOPAMINE D2 SELECTIVE IMAGING AGENT

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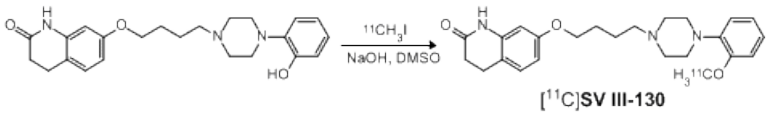
Objectives: The D_2 receptor is one subtype of the dopamine D_2-like class of receptors, which includes the D_2, D_3 and D_4 receptors. Although numerous radiotracers have been developed for imaging dopamine D_2 receptors, all D_2 receptor imaging studies use radiotracers having a similar affinity for both D_2 and D_3 receptors. A number of recent studies have suggested that dopamine D_2 and D_3 receptors are regulated differently in a variety of CNS disorders. Therefore, it is necessary to have radiotracers possessing a high affinity and selectivity for D_2 versus D_3 receptors, and vice versa, in order to study the differential regulation of D_2 and D_3 receptors under conditions of increased (i.e., substance abuse, schizophrenia) or decreased (Parkinson's Disease) dopaminergic tone. We recently completed the synthesis and in vitro characterization of a series of (butyloxy)-3,4-dihydro-2(1H)-quinolinone, SV III-130, which displayed high affinity at D_2 receptors (Ki = 0.22 nM) and 65-fold selectivity for D_2 versus D_3 receptors. The goal of the current study was to initially evaluate [^{11}C]SV III-130 in microPET studies in rhesus monkeys.

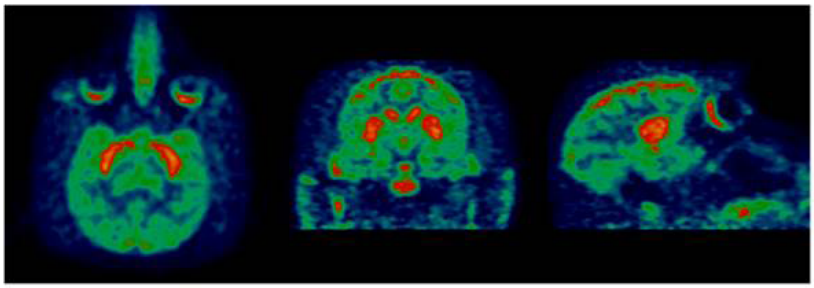
Methods: The synthesis of [^{11}C]SV III-130 was accomplished by alkylation of the des-methyl precursor with [^{11}C]methyl iodide in DMSO using aqueous sodium hydroxide as a base catalyst. MicroPet imaging studies was performed in rhesus monkeys using a Siemens Focus 220 microPet scanner following i.v. administration of ~10 mCi of [^{11}C]SV III-130.

Results: The radiolabeling yield was >60% overall. The radiochemical purity was >95% and the specific activity was greater than 3,000 mCi/mmol. MicroPET imaging studies in rhesus monkeys indicated that the uptake of [^{11}C]SV III-130 was high in the caudate and putamen, which express a high density of dopamine D_2 receptors. The putamen : cerebellum ratio increased from unity (at the beginning of the MicroPET scanning) to reached a plateau value of ~2 at ~40 minutes post-injection (Figure1).

Conclusions: The results of this study indicated that [^{11}C]SV III-130 is a potential candidate for imaging dopamine D_2 (versus D_3) receptors in the CNS with PET.

Research Support: NIH grants (DA 16181 and NS 04056).





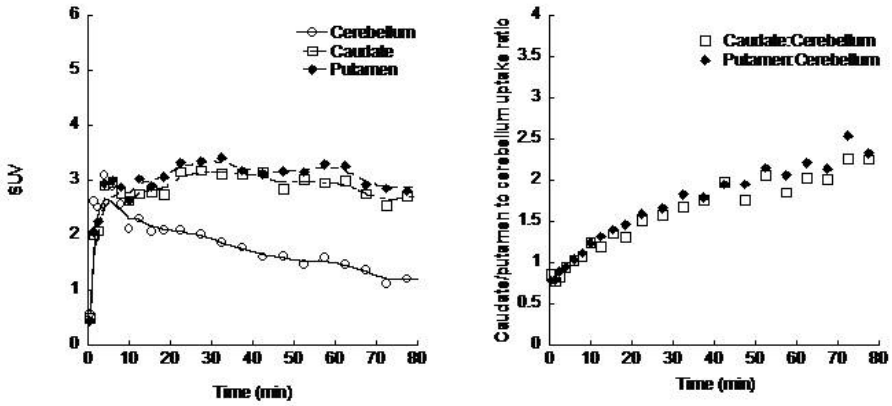


Figure 1. [^{11}C]**SV-III-130** microPET image on a representative Rhesus monkey. Top: MicroPET image on rhesus monkey brain; Bottom-left: tissue time-activity curves; Bottom-right: time radioactivity ratio curves of caudate and putamen to cerebellum.

ATOMOXETINE PRODUCES HIGH OCCUPANCY OF BOTH THE NOREPINEPRINE AND SEROTONIN TRANSPORTERS AT CLINICALLY RELEVANT DOSES IN NON-HUMAN PRIMATES: IMPLICATIONS ON TREATMENT OF DEPRESSION AND ADHD

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Objectives: Atomoxetine (ATX) is a norepinephrine transporter (NET) reuptake inhibitor and is used for treatment of depression and attention-deficit/hyperactivity disorder. It has a high affinity for norepinephrine transporter (NET); however, we previously demonstrated significant reductions in the binding of [^{11}C]DASB, a selective serotonin transporter (SERT) ligand, following 1.5 mg of ATX; a result similar to that achieved following a 2.0 mg dose of fluoxetine (a selective serotonin reuptake inhibitor, SSRI) [1]. Whether the therapeutic effects of ATX are due to inhibition of on one (NET) or two transporters (NET and SERT) is not known. Here we report our comparative PET imaging studies with [^{11}C]MRB (a selective NET ligand [2]) and [^{11}C] AFM (a SERT ligand [3]) to evaluate the in vivo IC_{50} of ATX for each individual transporter (NET and SERT) in non-human primates.

Methods: Rhesus monkeys were scanned up to four times with each tracer, twice a day (baseline and medium dose scans on day 1; low and high dose scans on day 2). ATX or saline (placebo) infusion began 2 h before each PET scan, lasting until the end of the 2-h scan. The final infusion rates ranged 0.01 - 0.12 mg/kg/h and 0.045 - 1.054 mg/kg/h for the NET and SERT studies, respectively. ATX plasma levels and metabolite corrected arterial input functions were measured. Distribution volumes (V_T) and IC_{50} values were estimated.

Results: ATX displayed dose-dependent occupancy on both NET and SERT. For NET, ATX IC_{50} was 27 ± 0.6 ng/mL plasma (corresponding to an infusion rate of 0.015 mg/kg/h), and 167±16 ng/mL plasma (corresponding to an infusion rate of 0.126 ± 0.013 mg/kg/h) for NET and SERT, respectively. Occupancy of 74% NET and 26% SERT was observed with ATX at 0.21 mg/kg. At a therapeutically relevant dose (1.8 mg/kg, equivalent to a plasma concentration of 600 ng/mL) ATX occupied ~80% of SERT.

Conclusions: Our data indicates an in vivo ATX IC_{50} ratio for SERT to NET of approximately 6, consistent with a reported in vitro affinity (Kd) ratio of approximately 4.5 (8.9 and 2 nM for SERT and NET, respectively) [4]. Based on these data, we propose that ATX at clinically relevant doses occupies high proportions of both NET and SERT. Thus, the interpretation of the therapeutic mode of action of ATX for treatment of depression and ADHD, may be more complex than selective blockade of the NET. Further studies to elucidate the mechanisms are needed. References: [1]. Ding Y-S and Fowler JS, NMB, 32:707-718, 2005. Review; [2]. Ding Y-S et al., Curr Pharm Design, 12:3871-45, 2006. Review; [3]. Huang Y et al., NMB, 31:543-556, 2004; [4]. Tatsumi et al., EJP, 340: 249-258, 1997.

INVESTIGATION OF ONE LABELED METABOLITE OF [11C]MADAM IN RAT AND MONKEY

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Objectives: [11C]MADAM is a radioligand suitable for PET studies of the serotonin transporter (SERT).[1,2] One of the important criteria for a suitable CNS PET tracer is that it should not produce labeled metabolites that enter the brain. Metabolite analysis in human and non-human plasma samples using HPLC separation have shown that [11C]MADAM was rapidly metabolized. A possible metabolic pathway is the S-oxidation which could lead to SOMADAM and SO_2MADAM. In vitro evaluation of these two potential metabolites have shown that SOMADAM exhibited a good affinity for SERT and a good selectivity for SERT over NET and DAT.[3] The aims of this study were twofold: (1) to measure the amount of [11C]SOMADAM in brain after [11C]MADAM injection into rat and (2) to evaluate [11C]SOMADAM as a potential radioligand for in vivo quantification of SERT in the monkey brain using PET. "

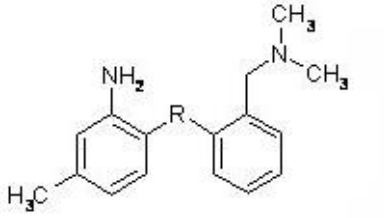

Figure 1. Chemical structure of MADAM, SOMADAM and SO_2MADAM.

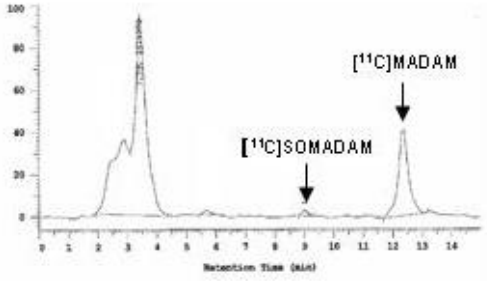

Figure 2. Radiochromatogram from HPLC analysis of monkey plasma at 15 min after injection of [11C]MADAM

Methods: [11C]MADAM and [11C]SOMADAM were obtained by N-[11C]methylation of the corresponding N-desmethyl precursors with [11C]methyl triflate in acetone. Sprague-Dawley rats were injected with [11C]MADAM and sacrificed at various time-points after injection. Radiometabolites in brain samples were studied using reverse phase HPLC. Comparative PET imaging studies in cynomolgus monkey with [11C]MADAM and [11C]SOMADAM were carried out and plasma samples were analyzed using reverse phase HPLC.

Results: The incorporation of [11C]methyl triflate to [11C]MADAM and [11C]SOMADAM was 52-75% and after purification by reverse phase HPLC, [11C]MADAM and [11C]SOMADAM were obtained with a radiochemical purity higher than 99%. HPLC analysis of brain sample after [11C]MADAM injection to rats demonstrated that [11C]SOMADAM was not detected in the brain. PET imaging studies in monkey using [11C]SOMADAM indicated that this tracer does not bind with high amounts to brain regions known to be rich in SERT. The fraction of [11C]SOMADAM in monkey plasma was approximatively 5% at 4 min and 1% at 15 min after [11C] MADAM injection.

Conclusions: [11C]SOMADAM was not detected in rat brain and is only a minor labeled metabolite of [11C]MADAM measured in monkey plasma. In addition, [11C]SOMADAM is not superior over [11C]MADAM as a SERT PET radioligand.

References: 1-Halldin C, Lundberg J, Svg J, Gulys B, Guilloteau D, Vercouillie J, Emond P, Chalon S, Tarkiainen J, Hiltunen J, Farde L, Synapse 2005. 2-Lundberg J, Odano I, Olsson H, Halldin C, Farde L, J Nucl Med. 2005. 3-Vercouillie J, Mavel S, Galineau L, Ragusa T, Innis R, Kassiou M, Chalon S, Doll F, Besnard JC, Guilloteau D, Emond P, Bioorg Med Chem Lett., 2006.

IMPROVED BRAIN UPTAKE OF 99MTCN-NOET LOADED BY TARGETED STERICALLY STABILIZED LIPOSOMES IN ICR MICE

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Objectives: Low brain uptake of ^{99m}Tc labeled receptor-based radiotracer in CNS is one of the bottlenecks of its applications in clinic. Moreover, ^{99m}Tc labeled radiotracer for brain tumor imaging also meets the difficulty of crossing the blood brain barrier. It was reported that RMP-7 conjugated with sterically stabilized liposomes could be used as an effective drug delivery system. In order to provide the molecular probes for early diagnosis of brain tumors, the neutral ^{99m}TcN-NOET, which is a potential tumor imaging agent, was selected to be loaded by the above targeted liposomes (SSLT).

Methods: ^{99m}TcN-NOET was prepared from the NOET kit, which is kindly provided by Beijing Shihong Pharmaceutical center. Soybean phospholipids, cholesterol and ^{99m}TcN-NOET were used to prepare the conventional liposomes by the thin film method. Then DSPE-PEG-RMP-7 was incorporated into the membrane of conventional liposomes by incubation at r. t. for 1 h to form targeted liposomes solution (^{99m}TcN-NOET-SSLT) with opalescence. The biodistribution of ^{99m}TcN-NOET and ^{99m}TcN-NOET-SSLT was investigated in ICR normal mice (18~20 g). The pharmacokinetic parameters were calculated with WinNonLin software.

Results: The radiochemical purity of ^{99m}TcN-NOET was higher than 99% evaluated by HPLC after the purification with CH_2H_2 extraction. 20-30 nm uniform size of ^{99m}TcN-NOET-SSLT could be observed under SEM. The brain uptake of ^{99m}TcN-NOET was 1.82 ± 0.19, 1.51 ± 0.21, 1.02 ± 0.08, 0.66 ± 0.07, and 0.55 ± 0.19 %ID/g at 2, 5, 15, 30, and 60 min p.i., respectively, while the brain uptake of ^{99m}TcN-NOET-SSLT was 3.62 ± 0.33, 2.51 ± 0.36, 2.20 ± 0.17, 1.55 ± 0.31, and 0.77 ± 0.10 %ID/g at the respective points of time . The pharmacokinetic parameters are shown in Table 1. The values of AUC (area under the tissue concentration time curve) and C_{max} (maximum concentration) of ^{99m}TcN-NOET-SSTL both in blood and brain are higher than that of ^{99m}TcN-NOET, while the CL (clearance rate) values of ^{99m}TcN-NOET-SSTL are lower than that of ^{99m}TcN-NOET. Therefore, ^{99m}TcN-NOET-SSTL demonstrated improved brain uptake and longer circulation in blood compared with ^{99m}TcN-NOET.

Conclusions: The brain uptake of ^{99m}TcN-NOET loaded by the targeted liposomes could be improved. It is reasonable to further apply SSLT for increasing the brain uptake of ^{99m}Tc-labeled receptor-based radiotracers.

Research Support: This work was supported by NSFC (No. 20501004 and No. 20871021).

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Table 1. Pharmacokinetic parameters in ICR mice (n=5-6)

	^{99m}TcN-NOET		^{99m}TcN-NOET -SSLT	
tissues	blood	brain	blood	brain
AUC(ID%•g^{-1}•min)	172	96.1	221	133
T_{max}(min)	2	2	2	2
C_{max}(ID%•g^{-1})	3.388	1.791	6.383	3.018
CL(ID%•g^{-1}•min^{-1})	0.0180	0.0380	0.0159	0.0325