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^{18}F-Fluorodeoxyglucamines: Reductive amination of hydrophilic ^{18}F-fluoro-2-deoxyglucose with lipophilic amines for the development of potential PET imaging agents

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Abstract

Maillard reaction of ^{18}F-FDG with biological amines results in the formation of ^{18}F-fluorodeoxyglycosylamines (^{18}F-FDGly) as pseudo-Amadori products. To increase in vivo stability, we report the reductive amination of FDGly to provide reduced fluorodeoxyglucamines (FDGlu). ^{18}F-Fluorodeoxyglucamines (^{18}F-FDGlu), resulting from linking ^{18}F-FDG (hydrophilic) to lipophilic molecules containing amine group may be useful as positron emission tomography (PET) imaging agents. Two amine derivatives, 7-chloro-8-hydroxy-3-methyl-l-(3'-aminophenyl)-2,3,4,5-tetrahydro-lH-3-benzazepine (SCH 38548 for dopamine D1 receptors) and BTA-0 (for Aβ amyloid) were reacted with FDG under reductive amination conditions to yield stable products, FDGluSCH and FDGluBTA. FDGluSCH had high binding affinity to rat brain dopamine D1 receptors with a K_i of 19.5 nM while FDGluBTA had micromolar affinity for human frontal cortex Aβ plaques. ^{18}F-FDGluSCH was prepared in low to modest radiochemical yields and preliminary results showed binding to the rat striatum in brain slices. In vivo stability of ^{18}F-FDGluSCH needs to be determined. Our results suggest that ^{18}F-FDG is a useful "radioactive synthon" for PET radiotracer development. Its usefulness will have to be determined on the basis of the structure-activity relationship of the target molecule.

Abstract

^{18}F-Fluorodeoxyglucamines were synthesized as a potential new avenue for PET radiotracer development, where lipophilicity of the radiotracer may be an issue. The rapid linkage of ^{18}F-FDG to the biological amine of interest was tested to synthesize the dopamine D1 receptor radiotracer, ^{18}F-FDGluSCH which showed good biological properties.

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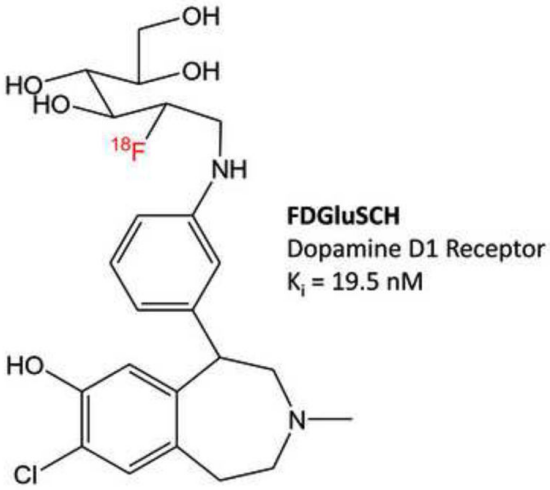

FDGluSCH
Dopamine D1 Receptor
K_i = 19.5 nM

Keywords

Dopamine D1 receptor; PET; Imaging; ^{18}F-FDG; ^{18}F-Fluorodeoxyglucamine

Reductive amination has been used as a method in synthesizing various molecules involved in human physiology. Antigens have been prepared and tested in rabbits by coupling carbohydrates to proteins through reductive amination.[1] A triple reductive amination strategy has also been investigated to synthesize pyrrolizidine alkaloids, which display biological activity such as glucosidase inhibition, anti-HIV potency and can play a necrotic and allergic role against living organisms.[2,3] In addition, Maillard reaction and reductive amination have been used in combination to synthesize potential protein cross-linkers.[4] Thus, products of reductive amination can be of great biological significance, for drug delivery as prodrugs, role in the central nervous system (CNS) and other potential applications.

We have previously reported the Maillard reaction of ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG, **1** Fig-1) with biological amines resulting in the formation of ^{18}F-fluorodeoxyglycosylamines (^{18}F-FDGly, **3** Fig-1) as quasi-Amadori products.[5] FDGly is formed as a Schiff base in the Maillard reaction and due to the presence of fluorine at the 2 position it does not progress to the classical Amadori product.[6] This Schiff base can rearrange between the cyclized **3** and the open form **4** (Fig-1), which may make it susceptible for faster degradation in vivo. Thus, reductive amination of ^{18}F-FDGly with biological amines at the 1 position is necessary. The reduction of the Schiff base results in fluorodeoxyglucamine **5** (^{18}F-FDGlu) (Fig-1). Reductive amination allows linking hydrophilic (^{18}F-FDG) to a lipophilic (amine) molecule, which may be useful in optimizing the non-specific binding of the resulting radiotracer for in vivo imaging.

In this preliminary study, we have applied this “FDG linker” approach to the study of two targets, the dopamine D1 receptors and the Aβ-amyloid plaques. Radiotracers for dopamine D1 receptors have been developed using the synthesis of FDGlu. Dopamine D1 receptors

are involved in cognition and memory,[7,8] movement disorders,[9] and other CNS functions. SCH 23390 and NNC112 are previously investigated dopamine D1 receptor C-11 PET imaging agents.[10, 11] These radiotracers have a short physical life (labeled with C-11, half-life 20.4 min) (**6**, Fig. 2). In addition, ^{11}C-SCH23390 has been shown to have a short biological half-life and selectivity is affected by its affinity for 5-HT2 receptors.[12,13] Due to the continued interest in the imaging of dopamine D1 receptors, we have explored SCH 38548, an analog of SCH23390 and shown that (*R*)-*N*-(3-^{18}F-fluoropropyl)SCH 38548 has promise as a dopamine D1 receptor radiotracer, but could gain from an improved in vivo properties.[14] Thus, the FDG linker product of SCH 38548 and FDG to synthesize 7-chloro-8-hydroxy-3-methyl-l-(3'-fluorodeoxyglucaminophenyl)-2,3,4,5-tetrahydro-lH-3-benzazepine **7** (FDGluSCH) is reported here. Additionally, preliminary biological evaluation of FDGluSCH and the radiolabeled analog, ^{18}F-FDGluSCH were also carried out.

A number of efforts have now been made to prepare fluorine-18 analogs and reduce nonspecific binding of the radiotracers for imaging Aβ plaques and neurofibrillary tangles.[15] Because the well-known agent 2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (^{11}C-6-OH-BTA, **8** Fig-2) binds to Aβ plaque, useful for Alzheimer's disease (AD) imaging,[16] we have investigated the FDG linker analog of ^{11}C-6-OH-BTA as a potential agent for targeting the Aβ plaques. Thus, 2-(4'-fluorodeoxyglucaminophenyl)-6-hydroxybenzothiazole **9** (FDGluBTA) was synthesized and tested for affinity to human Aβ plaque.

Reduction of fluorodeoxyglycosylamines (FDGly) using sodium cyanoborohydride ($NaCNBH_3$) was successful in providing fluorodeoxyglucamine (FDGlu) products at room temperature that were isolated in moderate to high yield. The coupling of amines with FDG was improved by reductive amination because the reversibility of the Schiff base reaction was removed upon reduction. The reductive amination of SCH38548 and FDG successfully provided FDGluSCH in high yield. [17] The fluorodeoxyglycosylamines, FDGBTA was previously synthesized as an analog of PIB, which is known to bind to human Aβ plaques.[5] Here, stable fluorodeoxyglucamine product, FDGluBTA was successfully synthesized in >90% yield.[18] Yields of some other substituted amines (not shown here) were less promising and may be an indication of the need for appropriate basicity of the amine in order to form the adduct.

[17]All chemicals and solvents were of analytical or HPLC grade from Aldrich Chemical Co. and Fisher Scientific. Electrospray mass spectra were obtained on a Model 7250 mass spectrometer (Micromass LCT). Proton NMR spectra were recorded on a Bruker OMEGA 500 MHz spectrometer. Analytical thin layer chromatography (TLC) was carried out on silica coated plates (Baker-Flex, Phillipsburg, NJ). Chromatographic separations were carried out on preparative TLC (silica gel GF 20×20 cm 2000 micron thick; Alltech Assoc. Inc., Deerfield, IL) or silica gel flash columns or semipreparative reverse-phase columns using the Gilson high performance liquid chromatography (HPLC) systems. FDGluSCH: For the synthesis of FDGluSCH, 3.3 mg (1.10×10^{-5} mole) SCH 38548 and 8.3 mg (4.56×10^{-5} mole) FDG were dissolved in 1.0ml MeOH, 40μl acetic acid, 83 mg molecular sieves and 60 mg $NaCNBH_3$. The solution was stirred at room temperature for 48 hours. Molecular sieves were filtered and $NaHCO_3$ powder was added. Preparatory TLC was performed using 1:1 dichloromethane-methanol to provide pure FDGluSCH in high quantitative yield. MS: m/z 469 $[M+H]^+$. NMR δ ppm (CD_3OD): 7.10 (d, 2H), 6.60 (s, 1H), 6.35 (s, 2H), 6.20 (s, 1H), 4.40 (dd, 1H, CHF), 4.10 (d, 1H, ArCHAr), 3.5-3.9 (br, 6H), 2.85 (br, 6H), 2.25 (s, 3H, NCH_3). Retention time of SCH 38548 was 15 mins while that of FDGluSCH was 11 mins (reverse-phase 10 μm C-18 Econosil HPLC column, 10×250 mm (from Alltech Assoc. Inc., Deerfield, IL), 40% 0.1% triethylamine in water-60% acetonitrile, flow rate 1.5 mL/min).

[18]FDGluBTA: For the synthesis of FDGluBTA, 3.0 mg (1.24×10^{-5} mole) desmethyl 6-OH-BTA and 2.3 mg (1.24×10^{-5} mole) FDG were dissolved in 0.5ml MeOH, 40μl acetic acid, 80 mg molecular sieves and 8 mg $NaCNBH_3$. The solution was stirred at room temperature for 48 hours. Molecular sieves were filtered and preparatory TLC was performed using 9:1 dichloromethane-methanol to provide pure FDGluBTA in >90% yield. MS: m/z 431 $[M+Na]^+$. NMR δ ppm (CD_3OD): 7.78 (dd, 2H), 7.70 (d, 1H), 6.94 (dd, 2H), 6.77 (d, 2H), 6.20 (s, 1H), 4.30 (dd, 1H, CHF), 3.5-3.9 (br, 6H).

A competition binding assay of FDGluSCH for dopamine D_1 receptors in rat brain slices using ^{3}H-SCH 23390 autoradiography showed strong binding and the graph generated had a sigmoidal shape (Fig-3A).[19] The measured IC_{50} of FDGluSCH was 5.2×10^{-8} (Ki = 19.5 nM; calculated using K_d of 0.6 nM for ^{3}H-SCH 23390)[14] and is in the range of some of the previously developed analogs of SCH 38548, but weaker than the parent SCH 38548. The displacement of ^{3}H-SCH 23390 by FDGluSCH from the rat striatum and frontal cortex suggest that FDGluSCH is stable in vitro and exhibits binding properties similar to SCH 23390. The effect of the hydrophilic FDG on the molecule is not detrimental to the receptor binding properties of FDGluSCH.

Postmortem human AD brain homogenates were used for competition binding assay of FDGluBTA with ^{3}H-PIB on for Aβ plaques binding was carried out.[20] Displacement binding study of ^{3}H-PIB provided an IC_{50} for PIB of 1.9×10^{-8}, whereas FDGluBTA had an IC_{50} of 5×10^{-6} (Fig-3B). These results show that FDGluBTA has a 100 times weaker binding affinity for the “PIB binding site” compared to PIB suggesting that the hydrophilic FDG instead of the “methyl” group in PIB is not well tolerated in this molecule. Our previous findings with the fluorodeoxyglycosylamine, ^{18}F-FDGBTA suggested grey matter binding to regions of postmortem human AD hippocampal slices which were somewhat similar to ^{11}C-PIB, but ^{18}F-FDGBTA was nonuniform.[5] Thus, although FDGluBTA showed weak affinity for ^{3}H-PIB in the homogenate binding assay, further studies with this derivative may have to be considered for possible binding to neurofibrillary tangles instead of Aβ plaques.[21]

Since FDGluSCH exhibited good affinity for the dopamine D1 receptors, radiolabeling of this derivative to provide a potential PET imaging agent, ^{18}F-FDGluSCH was undertaken.[22]

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[19]Rat brain slices were obtained on a Leica 1850 cryotome. Fluorine-18 and tritium autoradiographic studies were carried out by exposing tissue samples on storage phosphor screens. The apposed phosphor screens were read and analyzed by OptiQuant acquisition and analysis program of the Cyclone Storage Phosphor System (Packard Instruments Co., Boston, MA). All animal studies were approved by the Institutional Animal Care and Use Committee of University of California-Irvine. Rat cortex sections (10 μm thick) were preincubated in the D1 buffer (50mM Tris HCl, 2 mM $CaCl_2$-$2H_2O$, 120 mM NaCl, 1 mM $MgCl_2$-$6H_2O$, and 5 mM KCl, pH 7.4) for 10 minutes. ^{3}H-SCH 23390 (1 nM) was added in each chamber. The brain sections were placed in a glass chamber and incubated with FDGluSCH in the D1 buffer at different concentrations (10^{-8} to 10^{-5}), at 37°C for 90 minutes. The slices were then washed with cold buffer (2×3 minutes) and cold deionized water 1 min. Slides were then air-dried and exposed to phosphor screen for 25 days. The autoradiographs were generated using the Phosphor Cyclone Imager. The amount of binding was evaluated in digital light units (DLU/mm^2) using OptiQuant acquisition and analysis program (Packard Instruments). Data were analyzed using the following procedures: (a) the background binding of FDGluSCH was subtracted for all samples; (b) the specific binding was normalized to 100% (no competitive ligand); and (c) the binding isotherms were fit to the Hill equation (KELL BioSoft software [v 6], Cambridge, U.K.). The measured IC_{50} was converted to K_i by the Cheng-Prusoff equation, using K_d of ^{3}H-SCH 23390 as 0.6 nM as described previously.[14]

[20]Human brain homogenate assays using FDGluBTA were performed to measure the binding affinity of FDGluBTA to AB-amyloid plaques. The cerebrum of the human brain was isolated and homogenized in assay buffer for 30 s (PBS Buffer, 10% alcohol, pH7.4) using Tekmar tissumizer (15 s, half maxima speed). The supernatant was removed and the pellet was diluted with incubation buffer. A fixed concentration of ^{3}H-PIB was incubated with the human homogenate in the presence of various concentrations of FDGluBTA (10^{-11} to 10^{-4}) in the assay buffer. Nonspecific binding was determined by including PIB. Total assay volume was 0.25 mL. To start, 0.1 mL of the human brain homogenate was added to each test tube containing ^{3}H-PIB and different concentrations of FDGluBTA. The assay was done in duplicate and all test tube samples were incubated for 1 h in a 37°C water bath. After incubation, a rapid vacuum filtration was implemented through Whatman GF/C filter paper (presoaked in 0.1% polyethylamine in 10 mL of millipore water) using a Brandel tissue harvester. The filter was washed three times with 5 mL of cold buffer, was transferred to vials with 5 mL Bio-Safe II scintillation cocktail, and counted for 10 min in a scintillation counter. Data were analyzed using the following procedures: (a) the nonspecific binding of ^{3}H-PIB was subtracted for all samples; (b) the specific binding was normalized to 100% (no competitive ligand); and (c) the binding isotherms were fit to the Hill equation (KELL BioSoft software [v 6], Cambridge, U.K.).

[21]Okamura, N.; Furumoto, S.; Fodero-Tavoletti, M.T.; Mulligan, R.S.; Harada, R.; Yate, P.; Pejoska, S.; Kudo, Y.; Master, C.L.; Yanai, K.; Rowe, C.C.; Villemagne, V.L. (2014). Non-invasive Assessment of Alzheimer’s Disease Neurofibrillary Pathology using ^{18}F-THK2105 PET. *Brain.* **2014**, *137*, 1762.

Commercially available ^{18}F-FDG was obtained in a 0.9% saline solution, and both aqueous and nonaqueous (in the presence of molecular sieves) conditions were examined for the formation of ^{18}F-FDGluSCH. Formation of the Schiff base was improved by heating the mixture for 1 hour before $NaCNBH_3$ was added in order to produce the reduced ^{18}F-FDGluSCH. Purified ^{18}F-FDGluSCH was isolated using reverse-phase high performance liquid chromatography (HPLC), which showed distinct retention times for ^{18}F-FDG, SCH38548 and the synthesized product ^{18}F-FDGluSCH (Fig-4).[22] Reaction conditions are currently being investigated and optimized for higher radiochemical yield and better chromatographic separation.

Preliminary in vitro binding results in rat brain slices showed preferential binding of ^{18}F-FDGluSCH to the striatum of rat brain and was 2 times more than in the cerebellum (which contains few dopamine D1 receptors) (Fig-5B).[23] This binding of ^{18}F-FDGluSCH was displaced in the presence of unlabeled SCH 38548 (Fig-5C). The low striatum to cerebellum ratio may be due to the low radiochemical yield and low apparent specific activity due to contamination from the closely eluting mass peaks in the HPLC purification (Fig-4B). Thus, ^{18}F-FDGluSCH may have some potential for imaging dopamine D1 receptors in vitro and in vivo.

In conclusion, our results suggest that ^{18}F-FDGlu is stable in vitro and exhibits biological properties. The development of these derivatives potentially provides a new avenue for PET radiotracer development for the CNS, where lipophilicity is an issue. Additionally, it allows for the rapid linkage of an already ^{18}F-fluorine labeled synthon (^{18}F-FDG) to the biological amine of interest. However, it must be noted that yields of substituted amines varied significantly and the retention of biological properties would have to be tested on a case-by-case basis due to the structural needs of the binding site. This variability in properties is exemplified in this preliminary report where the dopamine D1 receptor binding site was amenable to accepting the FDG moiety in FDGluSCH and exhibited high affinity, whereas the binding site in Aβ plaque was not as seen with FDGluBTA which exhibited low affinity. Further studies are planned with ^{18}F-FDGluSCH in order to ascertain in vivo binding properties to the dopamine D1 receptor.

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[22] ^{18}F-FDG was obtained from PETNET in sterile saline solution. Fluorine-18 radioactivity was counted in a Capintec dose calibrator while low level counting was carried out in a well-counter (Cobra quantum, Packard Instruments Co., Boston, MA). Radioactive thin layer chromatographs were obtained by scanning in a Bioscan system 200 Imaging scanner (Bioscan, Inc., Washington, DC). ^{18}F-FDGluSCH: For the synthesis of ^{18}F-FDGluSCH, 0.5 mg (1.66×10^{-6} mole) SCH 38548 was dissolved in 0.5 mL MeOH and 0.25 mL of 2 to 5 mCi ^{18}F-FDG (in 0.9% sterile saline) was dissolved in the solution. 25mg $NaCNBH_3$ was added at 15 minutes of heating. The solution was heated for 1 hour at 105 °C. HPLC was used to isolate and purify ^{18}F-FDGluSCH, which had a retention time of 10 minutes (reverse-phase 10 μm C-18 HPLC column, 10×250 mm, 40% 0.1% triethylamine in water-60% acetonitrile, flow rate 1.5 mL/min). The purified ^{18}F-FDGluSCH was obtained in low radiochemical yield with specific activities of approx. 5.4 Ci/mmol. Radiochemical purity was >95%, however, the low apparent specific activity is due to the closely eluting mass peak after the product peak. This product was used for biological studies.

[23] Sprague Dawley Rat cortex sections (10 μm thick) were preincubated in the D1 buffer (50 mM Tris HCl, 2 mM $CaCl_2$-$2H_2O$, 120 mM NaCl, 1 mM $MgCl_2$-$6H_2O$, and 5 mM KCl, pH 7.4) for 10 minutes. The brain sections were placed in a glass chamber and incubated with 5μCi ^{18}F-FDGluSCH split into total and non-specific in the D1 buffer at 37°C for 60 minutes. Non-specific binding was measured using 10 μM SCH 38548. The slices in both chambers were then washed with cold buffer (2×3 minutes) and cold deionized water 1 min. Slides were then air-dried and exposed to phosphor screen for 24 hours. The autoradiographs were generated using the Phosphor Cyclone Imager. The amount of binding was evaluated in digital light units (DLU/mm^2) using OptiQuant acquisition and analysis program (Packard Instruments). Data were analyzed using the following procedures: (a) the background binding of ^{18}F-FDGluSCH was subtracted for all samples by drawing regions of interest; (b) using excel to graph the results obtain by drawing regions of interest at the striatum of both the non-specific and the total.

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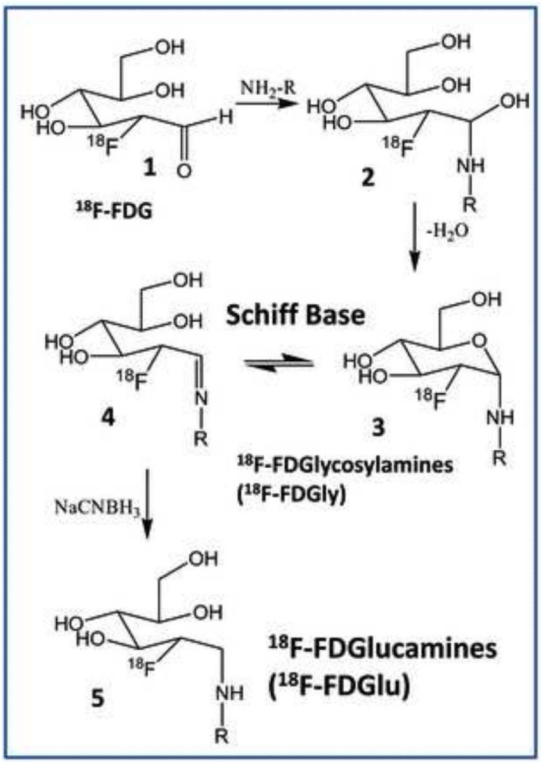

Figure-1.

Generic synthesis scheme of ^{18}F-FDG **(1)** with amine leading to formation of ^{18}F-fluorodeoxyglcosylamines (^{18}F-FDGly; cyclic **3** and open **4**). Reduction of the Schiff base with sodium cyanoborohydride ($NaCNBH_3$) led to ^{18}F-fluorodeoxyglucamine, ^{18}F-FDGlu **(5)**.

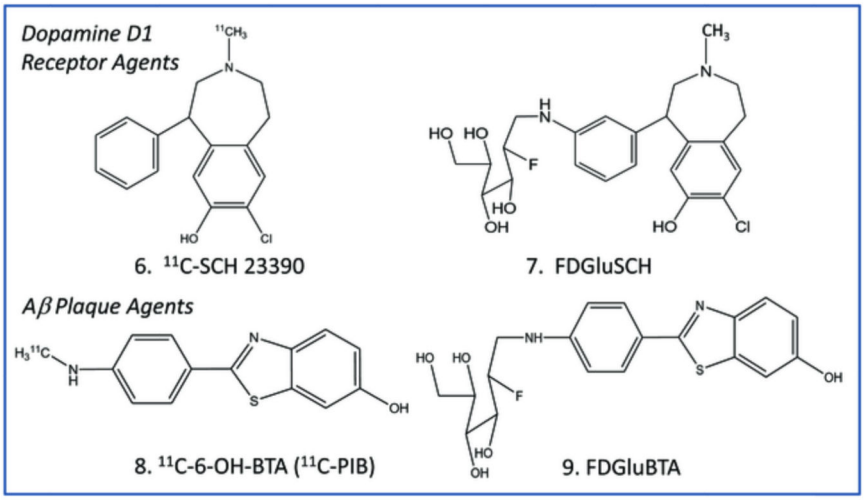

Figure-2.

Chemical structure of dopamine D1 receptor imaging tracer, ^{11}C-SCH 23390 (**6**) and fluorodeoxyglucose analog, FDGluSCH (**7**). Chemical structure of Aβ plaque imaging tracer, ^{11}C-6-OH-BTA (**8**) and fluorodeoxyglucose analog, FDGluBTA (**9**).

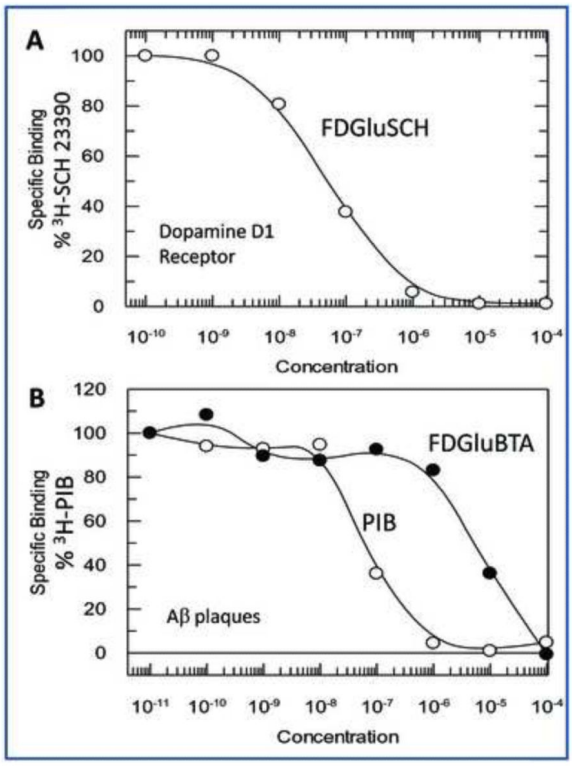

Figure-3.

(A) Binding affinity curve from competition assay of FDGluSCH with ^{3}H-SCH23390 labeled dopamine D1 receptors in the striatum of rat brain slices. (B) Binding affinity curve from competition assay of 6-OH-BTA (PIB) and FDGluBTA with ^{3}H-PIB labeled Aβ plaques in homogenates of postmotem human brain frontal cortex of AD subject.

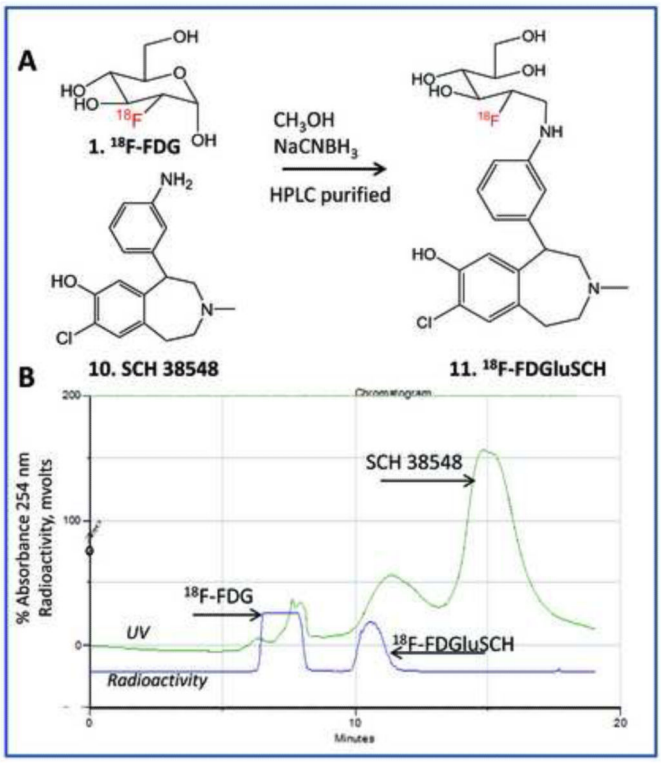

Figure-4.

(A) Reductive amination for the radiosynthesis of ^{18}F-FDGluSCH (**11**) showing reaction of ^{18}F-FDG **(1)** with SCH 38548 (**10**) in the presence of sodium cyanoborohydride ($NaCNBH_3$). (B) HPLC purification profile of reaction. The radioactive product, ^{18}F-FDGluSCH (**11**) eluted at 11 min while the starting materials SCH 38548 eluted at 15 min and ^{18}F-FDG eluted at 7 min.

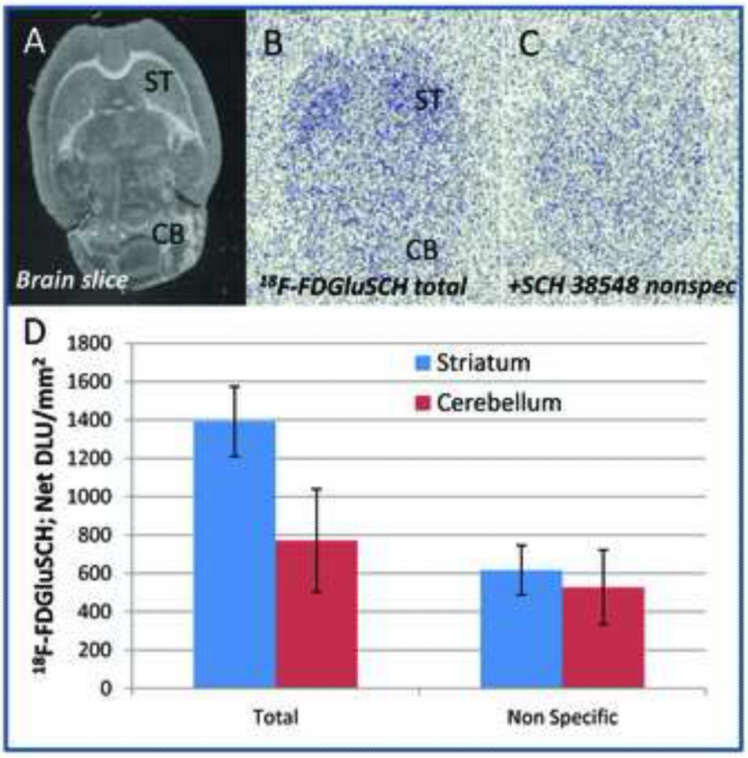

Figure-5.

(A) Scan of a 10 μm thick rat brain slice showing striatum (ST) and cerebellum (CB). (B) Autoradiograms showing binding of ^{18}F-FDGluSCH to the dopamine D1 receptor rich striatum while little binding was seen in the cerebellum. (C) Nonspecific binding measured in the presence of 10 μM SCH 38548 showing displacment of ^{18}F-FDGluSCH from the striatum. (D) Graph shows relative binding of ^{18}F-FDGluSCH under total (B) vs. non-specific (C) conditions based on autoradiographs in the striatum and cerebellum.