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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

Aparna Baranwal, Jogeshwar Mukherjee *

Preclinical Imaging, Department of Radiological Sciences, University of California-Irvine, Irvine, CA 92697, United States

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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.

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]

* Corresponding author at present address: B138 Medical Sciences, Department of Radiological Sciences, University of California-Irvine, Irvine, CA 92697-5000, United States. Tel.: +1 (949) 824 2018; fax: +1 (949) 824 2344.
E-mail address: j.mukherjee@uci.edu (J. Mukherjee).

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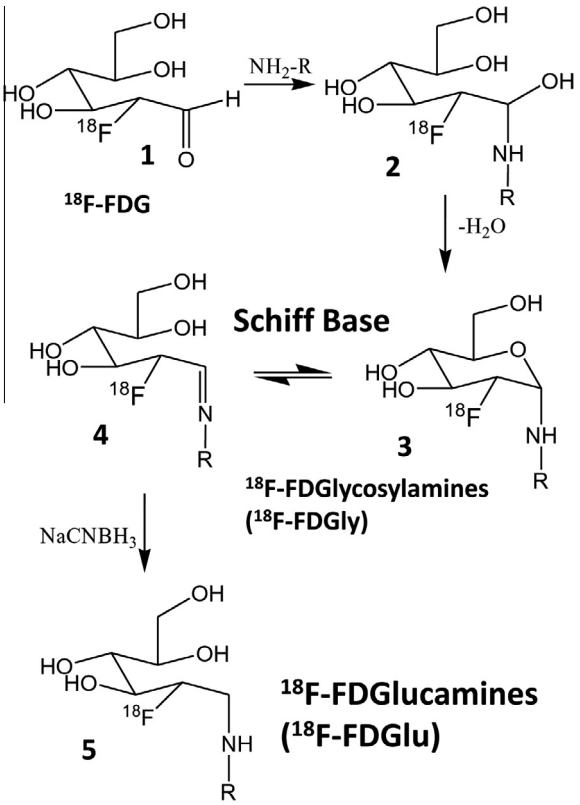

Figure 1. Generic synthesis scheme of ^{18}F-FDG (**1**) with amine leading to formation of ^{18}F-fluorodeoxyglcosylamines (^{18}F-FDGly; cyclic **3** and open **4**). Reduction of the Schiff base with sodium cyanoborohydride ($NaCNBH_3$) led to ^{18}F-fluorodeoxyglucamine, ^{18}F-FDGlu (**5**).

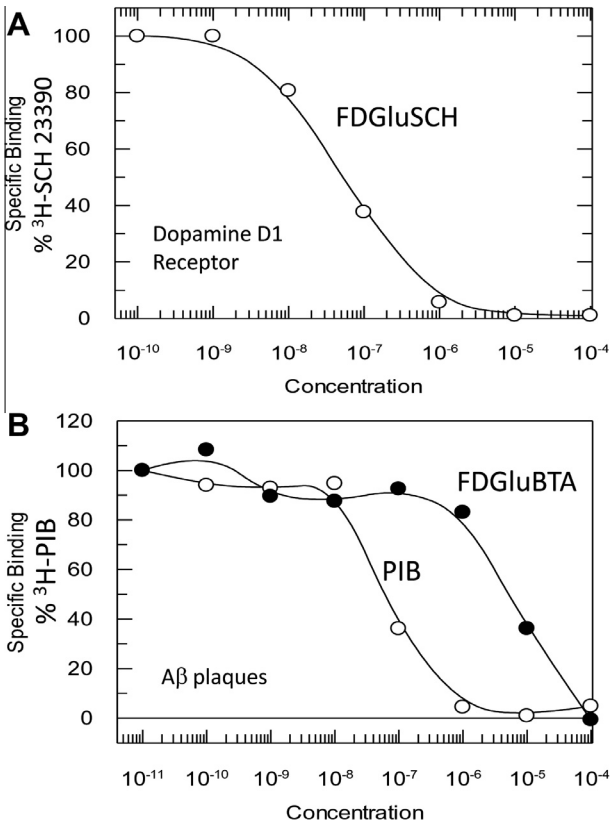

Figure 3. (A) Binding affinity curve from competition assay of FDGluSCH with ^{3}H-SCH23390 labeled dopamine D1 receptors in the striatum of rat brain slices. (B) Binding affinity curve from competition assay of 6-OH-BTA (PIB) and FDGluBTA with ^{3}H-PIB labeled Aβ plaques in homogenates of postmortem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

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

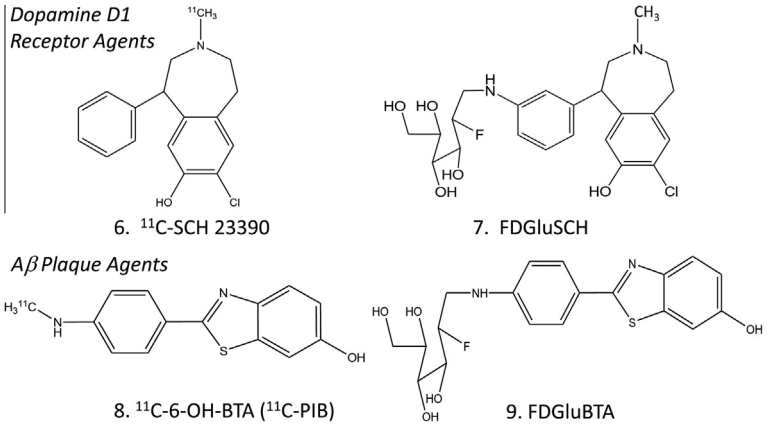

Figure 2. Chemical structure of dopamine D1 receptor imaging tracer, ^{11}C-SCH 23390 (**6**) and fluorodeoxyglucose analog, FDGluSCH (**7**). Chemical structure of Aβ plaque imaging tracer, ^{11}C-6-OH-BTA (**8**) and fluorodeoxyglucose analog, FDGluBTA (**9**).