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Research Article

Synthesis of [^{18}F]-6-deoxy-6-fluoro-D-glucose ([^{18}F]6FDG), a potential tracer of glucose transport

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Summary

With the goal of developing a PET radioligand for the *in vivo* assessment of glucose transport, 6-deoxy-6-[^{18}F]fluoro-D-glucose ([^{18}F]6FDG) was prepared in two steps from $^{18}F^-$. Starting with D-glucose, the tosyl- and mesyl-derivatives of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose were prepared by known methods. Reaction of either of these precursors with $^{18}F^-$ resulted in the formation of 3,5-*O*-benzylidene-6-deoxy-6-[^{18}F]-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose in high yield. Subsequent hydrolysis resulted in the production of [^{18}F]6FDG. Under optimal conditions, [^{18}F]6FDG is produced 60–70 min after end of bombardment (EOB) in 71 ± 12% yield (decay corrected, based upon fluoride) with a radiochemical purity of ⩾96%. Preliminary experiments have indicated that [^{18}F]6FDG may be a more representative *in vivo* tracer for the glucose transporter than 2FDG. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: fluorine-18; 6-deoxy-6-[^{18}F]fluoro-D-glucose; 2FDG; glucose transport

Introduction

Glucose is the main source of energy for mammalian cells and plays a central role in the metabolic system responsible for normal biological function. The *in vivo* assessment of glucose transport is of major clinical importance because abnormalities in glucose transport have been associated with various

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pathological conditions such as diabetes mellitus,[1,2] Alzheimer's disease,[3–5] Huntington's disease[6] and the biochemistry of various tumors.[7]

The development of a suitable radioligand for PET would assist in the assessment of glucose transporters *in vivo*, allowing investigation of the crucial role of these transporters in glucose homeostasis. The assessment of glucose uptake in tissues (transport and/or phosphorylation) is possible by imaging with 2-deoxy-2-[^{18}F]fluoro-D-glucose (2FDG). Results with 2FDG are sometimes contradictory because alteration of the transport and phosphorylation steps may develop independently with different pathologies, even in offsetting directions, while direct distinction between these two steps is not possible.[8,9] In one study of the effect of insulin on glucose blood-brain barrier transport,[10] and in another study to estimate rates of transport in insulin resistance and diabetes,[11] it was necessary to account for the phosphorylation of 2FDG in addition to transport. 3-*O*-Methyl-D-glucose (3-OMG) is a glucose analog that enters the cell by glucose transport but is not phosphorylated, thus allowing transport rates to be measured without the complications of subsequent metabolism of the tracer.[12–14] This tracer has been labeled with carbon-11 and used for *in vivo* studies of glucose transport in the brain and the heart.[15–19] Despite the favorable characteristics of 3-OMG, its usefulness is limited by the short half-life of carbon-11 (20 min), which probably explains the small number of studies with this tracer. Recently, the uptake of the α- and β-anomers of ^{11}C-methyl-D-glucose (MG) in mouse kidney has been reported,[20] and the potential of MG as a tracer for sodium-dependent glucose transporters (SGLTs) merits further study.

Two radiolabeled versions (^{123}I and ^{125}I) of 6-deoxy-6-iodo-D-glucose (6IDG) have been suggested as potential imaging agents of glucose transport.[21,22] It was reported that [^{123}I]6IDG was responsive to insulin in *in vitro* preparations, but not in isolated rat heart,[21] and that [^{123}I]6IDG was able to detect a defect in glucose transport in db/db diabetic mice.[22] However, uptake in brain and heart was lower than that of 3-OMG[23] and the usefulness of 6IDG as a tracer of glucose transport in selected organs in clinical applications has been questioned.[24]

Quite some time ago, one of us examined the structural requirements for active transport of glucose by intestine[25–27] and for stimulation of glucose transport in muscle by insulin.[28] 2-Deoxyglucose (2DG) was shown responsive to insulin but not transported by intestine, 3-OMG and 3-deoxyglucose were responsive to insulin and actively transported by intestine and 6-*O*-methylglucose was neither responsive to insulin nor transported by intestine. Galactose, α-methyl-D-glucose, and 6-deoxy-6-fluoro-glucose (6FDG) were found to be transported by intestine, but 6-deoxy-6-iodo-galactose was not. Thus, the structural requirements for insulin stimulated transport by muscle are different than for active transport by intestine. This work was done long

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before the facilitated glucose transporters (GLUTs) in several tissues and the SGLTs in the brush border of intestine and the proximal tubules were characterized.

As we developed an interest in assessment of glucose transport *in vivo*, we were led to consider 6-deoxy-6-[^{18}F]fluoro-D-glucose ([^{18}F]6FDG) as a potential tracer for glucose transport. 6FDG is subject to transport (*vide supra*), but because it lacks the 6-hydroxyl group, once inside the cell it cannot undergo phosphorylation at this position, which occurs as the next step in normal glucose metabolism. 6FDG competitively inhibits fermentation of glucose by intact yeast, but not yeast extracts.[29] Kinetic studies support the hypothesis that 6FDG and 2DG compete with glucose at the same transport site and that 6FDG does not affect any metabolic pathway in yeast cells.[30] Several 6-deoxy-6-[^{18}F]fluoro hexose analogs have been reported as potential PET tracers (although not necessarily of glucose transport), including 6-deoxy-6-[^{18}F]fluoro-L-fucose,[31–33] 6-deoxy-6-[^{18}F]fluoro-D-galactose[34–36] and 2,6-dideoxy-2-fluoro-6-[^{18}F]-fluoro-β-D-glucopyranosyl fluoride.[37] To our knowledge, [^{18}F]6FDG has not previously been reported.

Results and discussion

The preparation of unlabeled 6FDG by fluoride-ion displacement of a sulfonate group from the tosyl- and mesyl-derivatives of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose (**5** and **6**, respectively), followed by acidic hydrolysis of the protecting groups has been reported.[38,39] We prepared **5** and **6** from D-glucose by a slight modification of the published procedure,[38] as outlined in Scheme 1. Reaction of D-glucose with acetone employing sulfuric acid as catalyst formed 1,2–5,6 di-*O*-isopropylidene-D-glucofuranose, which was not purified but immediately subjected to acid hydrolysis to produce 1,2-*O*-isopropylidene-D-glucofuranose (**1**). Reaction of **1** with tosyl chloride or mesyl chloride resulted in the formation of 6-deoxy-1,2-*O*-isopropylidene-6-(4′-methylbenzene)sulfonyloxy-D-glucofuranose (**2**) or 6-deoxy-1,2-*O*-isopropylidene-6-methylsulfonyloxy-D-glucofuranose (**3**), respectively. Diol protection of **2** and **3** by reaction with benzaldehyde in the presence of zinc chloride produced 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-(4′-methylbenzene)sulfonyloxy-α-D-glucofuranose (**4**) and 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-methylsulfonyloxy-α-D-glucofuranose (**5**), respectively.

For convenience, reaction conditions typically used for the preparation of 2FDG from 1,3,4,6-*tetra*-acetyl-2-trifluoromethylsulfonyl-β-D-mannopyranose were examined to determine the suitability for production of [^{18}F]6FDG from **4** and **5**. Reaction of either precursor with $^{18}F^-$ resulted in the formation of the fluorinated intermediate **6**[38,39] in high yield. Based upon a very limited number of experiments, there was no observable difference in the

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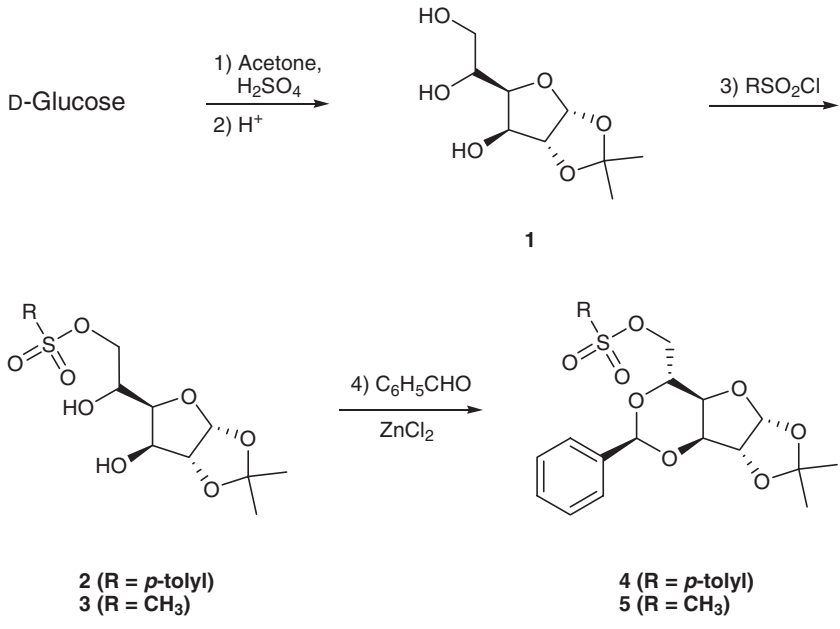

Scheme 1. Formation of the tosyl- and mesyl-derivatives of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose from D-glucose

yield of **6** from the tosylate **4** or the mesylate **5**; subsequent experiments employed **5** as precursor. Because of the relatively high yield from these initial experiments, the only further optimization of the synthetic procedure we undertook was to determine the minimum necessary amount of precursor in the reaction. When 5 mg precursor ($n = 3$) was used, **6** was obtained in $26 \pm 6\%$ chemical yield (range 17–29%); increasing the amount of precursor to 7.5–10 mg resulted in the production of **6** in $75 \pm 12\%$ yield (decay corrected, based upon fluoride, $n = 4$, range 58–86%).

Hydrolysis of **6** for 10 min in 1 N HCl at 110°C resulted in the formation of [^{18}F]6FDG. The hydrolysis yield was separately determined for only two experiments; yields of 69 and 95% were observed. It is likely that the 69% represents a lower limit of expected hydrolysis yield. The overall yield obtained from several subsequent experiments (*vide infra*) suggests the hydrolysis typically proceeds in high yield. Purification was achieved by passing the reaction mixture sequentially over small columns packed with C_{18} reversed-phase silica and neutral alumina. Product purity was determined by TLC and HPLC analysis. The [^{18}F]6FDG produced by this sequence was compared to an authentic sample of unlabeled 6FDG (Sigma Chemical). Analysis by TLC (co-spotting with labeled product) and HPLC found the authentic 6FDG to be identical to the labeled material. The conversion of **5** to [^{18}F]6FDG is shown in Scheme 2.

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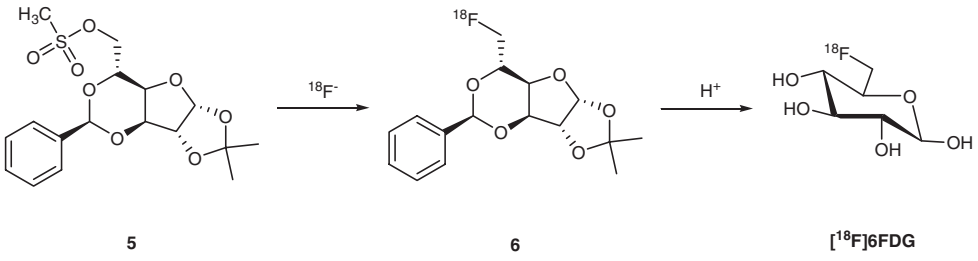

Scheme 2. Conversion of 5 to [^{18}F]6FDG

Under optimal conditions, [^{18}F]6FDG was obtained in two steps from $^{18}F^-$ in 71 $\pm$ 12% chemical yield ($n = 3$, range 58–80%). In one experiment starting with 1.37 GBq (37 mCi) of $^{18}F^-$, 0.733 GBq (19.8 mCi) of [^{18}F]6FDG (54% radiochemical yield, 80% chemical yield, based upon fluoride) was obtained 64 min after EOB with a radiochemical purity of 98%. Several production runs have been carried out remotely in a hot cell yielding 4.81–16.3 GBq (130–440 mCi) of [^{18}F]6FDG from 18.5 to 42.9 GBq (500–1160 mCi) of $^{18}F^-$ approximately 60–70 min after EOB in $\geqslant$96% radiochemical purity. By neutralization of the acidic hydrolysis reaction mixture with sodium hydroxide and sodium bicarbonate, dilution with sterile water for injection (USP) and sterile filtration through a 0.22 μm filter, the final product is obtained as a sterile, pyrogen-free and slightly hypertonic bicarbonate buffered saline solution, ready for injection. The final solution contains about 26 μmol of glucose from hydrolysis of the excess precursor. Under the standard reaction conditions, the glucose concentration in the final solution is approximately 8 mM (compared to 5.5 mM for the normal physiological concentration of glucose). The low level of glucose present is unlikely to have any consequence on experiments conducted with the 6FDG, especially considering that the solution is typically diluted several fold before administration.

Preliminary experiments to determine 6FDG uptake were carried out under basal conditions using two cell lines, Clone 9 cells[40,41] and 3T3 L1 adipocytes.[42] Uptake of 6FDG in Clone 9 cells was stimulated by azide addition; in 3T3 L1 adipocytes uptake was stimulated by insulin addition. In each cell line, uptake of 6FDG was found to be inhibited by cytochalasin B. The uptake of 6FDG was the same as uptake of 3-OMG (Dr F. Ismail-Beigi, personal communication). Glucose uptake in Clone 9 cells is by GLUT 1 transporters and in 3T3 L1 adipocytes GLUT 1 and GLUT 4 transporters; cytochalasin B is a specific inhibitor of the glucose transporters.

In other preliminary experiments in rats scanned in a small animal PET scanner, [^{18}F]6FDG was shown to lack the bladder uptake that is so characteristic of 2FDG images to such an extent that it was not possible to define the bladder on the images (Dr RF Muzic Jr, personal communication).

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This implies that, in contrast to 2FDG, [^{18}F]6FDG is a good substrate for the renal glucose transporter. In rats treated with phlorizin, which blocks the transporter and has no effect upon a 2FDG image, the [^{18}F]6FDG uptake in the bladder was similar to that of 2FDG.

These preliminary experiments, which will be completed and reported in detail elsewhere, indicate that [^{18}F]6FDG may be an effective substrate for glucose transport and would be a useful tracer for the assessment of alterations in glucose transporters.

Experimental

Reagents and solvents were obtained from Sigma-Aldrich Chemical Co. and Fisher Scientific and used without further purification unless otherwise noted. Acetonitrile was freshly distilled from calcium hydride prior to use. Thin layer chromatography (TLC) was carried out on E. Merck silica gel 60 F254 analytical plates. Radiation detection was performed with a Bioscan model AR-2000 thin layer plate reader using WinScan Version 3.07 software, and mass detection by UV light or in some cases acid charring. High performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1090 system with a photodiode array detector, a Beckman model 170 radiation detector and in some cases a Knauer model 198 refractive index detector. Elution conditions for TLC and HPLC varied and are specified individually for each compound below. 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-(4′-methylbenzene)sulfonyloxy-α-D-glucofuranose and 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-methylsulfonyloxy-α-D-glucofuranose (**4** and **5**, respectively) were prepared from D-glucose as previously reported,[38] with the exception that the reaction of glucose and acetone was catalyzed by sulfuric acid rather than $ZnCl_2$ (this alternate procedure was mentioned in the discussion section of the publication).

3, 5-*O*-benzylidene-6-deoxy-6-[^{18}F]-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (6)

$^{18}F-$ (obtained by 17 MeV proton bombardment of [^{18}O]H_2O[43]) was passed through anion exchange resin and [^{18}O]H_2O was recovered. $^{18}F-$ was eluted with aqueous potassium carbonate. An aliquot of this solution containing the desired quantity of radioactivity was transferred to a reaction vial containing ca. 12 mg (31.9 μmol) 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]hexacosane (Kryptofix 2.2.2, Kryptofix). If necessary, aqueous potassium carbonate solution was added in order to achieve the desired Kryptofix/K_2CO_3 mass ratio (5–6). The water was evaporated under reduced pressure at 110°C and dried by coevaporation with acetonitrile. A solution of 5–10 mg 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-(4′-methylbenzene)sulfonyloxy-α-D-glucofuranose (**4**, 10.8–21.6 μmol) or 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-

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isopropylidene-6-methylsulfonyloxy-α-D-glucofuranose (**5**, 12.9–25.9 μmol) dissolved in 100 μl anhydrous acetonitrile was added and the solution was heated for 10 min at 110°C. The reaction mixture was concentrated with gentle heating under a stream of Ar gas. The residue was mixed with 300 μl of ethyl acetate, followed by 900 μl of hexanes. The solution was passed over a small (ca. 150 mg) column of silica gel. The process was repeated with another 300 μl of ethyl acetate and 900 μl of hexanes. The solution was analyzed by TLC (developed twice with 4:1 hexanes:ethyl acetate; $R_f = 0.48$).

Hydrolysis of 3,5-O-benzylidene-6-deoxy-6-[^{18}F]-fluoro-1,2-O-isopropylidene-α-D-glucofuranose (**6**)

The solution of **6** described above was concentrated under a stream of Ar. To the dried residue was added 250 μl of 1 N HCl and the mixture was heated at 110°C for 10 min. After cooling, 125 μl of 2 N NaOH and 250 μl of 1 N $NaHCO_3$ were sequentially added and this solution was passed through a small column containing ~200 mg each of C_{18} reversed-phase silica and neutral alumina separated by a plug of glass wool. The reaction vial and small column were rinsed with 2 ml of water. The solution was analyzed by TLC (9:1 acetonitrile:water; $R_f = 0.45$) and HPLC (4.6 × 250 mm Alltech Econosphere NH_2 5 μ column, eluting with 90:10:0.01 acetonitrile:H_2O:40% aqueous CH_3NH_2 at 1 ml/min; $R_T = 8$ min). For comparison purposes, authentic 6FDG was analyzed by TLC (co-spotted with labeled product, detected by acid charring) and HPLC (refractive index detector) and found to have the same R_f and R_T as the hydrolysis product.

6-*deoxy-6-[^{18}F]fluoro*-D-*glucose ([^{18}F]6FDG)*

An aliquot containing 1.37 GBq (37 mCi) of $^{18}F-$ was added to a vial containing 12.4 mg (32.9 μmol) Kryptofix and 1.9 mg (13.7 μmol) K_2CO_3. The water was evaporated under reduced pressure at 110°C and dried by coevaporation with acetonitrile. A solution of 10.2 mg (26.4 μmol) 3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-6-methylsulfonyloxy-α-D-glucofuranose (**6**) dissolved in 200 μl anhydrous acetonitrile was added and the solution was heated for 10 min at 110°C. The reaction mixture was cooled, mixed with 750 μl of ethyl acetate and passed over a small (~150 mg) column of silica gel. The silica column was eluted with a second 750 μl aliquot of ethyl acetate. The solution was concentrated to dryness under vacuum at 80°C. To the residue was added 500 μl of 1 N HCl and this mixture was heated 10 min at 110°C. The reaction mixture was cooled and 250 μl of 2 N NaOH and 500 μl of 1 N $NaHCO_3$ were sequentially added. This solution was passed over a small column containing ~200 mg each of C_{18} reversed-phase silica and neutral alumina (separated with a glass wool plug) through a sterile filter into a

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suitable collection vial. The column was eluted with an additional 2 ml of sterile water to yield 0.733 GBq (19.8 mCi) of 6-deoxy-6-[^{18}F]fluoro-D-glucose as a sterile, pyrogen-free solution (by USP sterility and pyrogen testing procedures) 64 min after EOB (54% radiochemical yield, 80% chemical yield, based upon fluoride, 98% radiochemical purity). The solution was analyzed by TLC and HPLC as described above.

Conclusion

6-deoxy-6-[^{18}F]fluoro-D-glucose ([^{18}F]6FDG) was prepared in two steps from $^{18}F^-$. Starting with D-glucose, the tosyl- and mesyl-derivatives of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose were prepared by known methods. Reaction of either of these precursors with $^{18}F^-$ resulted in the formation of 3,5-*O*-benzylidene-6-deoxy-6-[^{18}F]-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose in high yield. Subsequent hydrolysis resulted in the production of [^{18}F]6FDG. Under optimal condition, [^{18}F]6FDG is produced in 71 ± 12% radiochemical yield (decay corrected, based upon fluoride) with a radiochemical purity of ⩾96% 60–70 min after EOB. Preliminary evaluation of 6FDG uptake by cell preparations *in vitro* and [^{18}F]6FDG in PET scans of rats indicates that 6FDG may be a good substrate for the glucose transporters and would be useful in assessment of variations in glucose transport independent of glucose phosphorylation.

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