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Synthesis and Preliminary Evaluation of [^{18}F]2-Deoxy-2,2-Difluoro-Glucose as a Potential PET Imaging Agent

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Summary

This paper describes the synthesis and preliminary *in-vivo* study of a new FDG analog, 2-deoxy-2,2-[^{18}F]difluoro-glucose (DFDG) for use as a potential imaging agent for PET. DFDG was prepared by the reaction of ^{18}F-acetyl hypofluorite on 3,4,6-tri-*O*-acetyl-2-fluoro-*D*-glucal followed by acid deprotection to give the final product in 27% decay corrected radiochemical yield. Biodistribution in mice showed rapid uptake in the heart (10% dose/gram) which remained relatively constant out to two hours. The brain uptake at 2 hours was 1.6% dose per gram. There was rapid clearance of activity from the blood after injection. Brain images in a Rhesus monkey showed a similar distribution when compared to FDG but with significantly more uptake in surrounding muscle.

Key Words: Positron emission tomography, fluoro-deoxy-glucose, glucose metabolism, acetyl hypofluorite

Introduction

The use of 2-deoxy-2-[^{18}F]fluoro-*D*-Glucose (FDG) to study glucose metabolism has seen extensive clinical applications especially in cardiology and oncology. Because of the growing importance of FDG/PET we decided to study close analogs of FDG, 2,2-dihalo-hexoses, as possible new PET and SPECT imaging agents. In addition to two 2-iodo-2-fluoro analogs (1) we have recently synthesized 2-deoxy-2,2-[^{18}F]difluoro-*D*-arabino-hexose (2-deoxy-2,2-[^{18}F]difluoro-glucose, DFDG), which has not previously been synthesized and evaluated. As well as being an untested, new, potential imaging agent we also hypothesized that the geminal fluorine atoms might give DFDG enhanced uptake in brain and heart tissue compared to FDG.

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2-Deoxy-2,2-difluoro-*D-arabino*-hexose (2-deoxy-2,2-difluoro-glucose) was first synthesised in 1971 by Adamson et.al (2). It has been shown to be a good substrate for hexokinase (K_M=0.13 mM, V_M=0.53) and has also been shown to strongly inhibit the growth in culture of lymphoma L5178Y cells. It was originally synthesized by the reaction of trifluoromethyl hypofluorite (CF_3OF) on acetylated 2-fluoro-glucal, therefore, it was expected that the reaction with acetyl hypofluorite would proceed in a similar manner. We now describe the synthesis and preliminary *in-vivo* evaluation of 2-deoxy-2,2-[^{18}F]-difluoro-glucose (DFDG).

Experimental

General

All reagents such as 30% HBr in acetic acid were purchased from Aldrich and used without further purification. All melting points (mp) are uncorrected. All nmr spectra (^{1}H, ^{19}F) were recorded on a 200 MHz Bruker AC200 (188 MHz for ^{19}F nmr spectra). All chemical shifts (δ) are reported in parts per million (ppm) down field from the standard and all coupling constants are in Hz. Thin layer chromatography was carried out on Merck Kieselgel gel 60 F_{254} plates and radio-tlc was carried out on a BioScan QCscan tlc plate scanner. Radioactivity was quantified by a Capintec Radioisotope Calibrator CRC-543X. [^{18}F]Acetyl hypofluorite was prepared from ^{18}F-F_2 as described by Jewet et.al. (3).

Biodistribution was performed in mice (4-6 week old, UBC, CD-1) using a tail vein injection. Animals were killed under ether anesthesia at various time points. Organs were dissected and counted and the results are expressed in percent administered dose per gram of tissue (% dose/gram).

Synthesis of 3,4,6-Tri-*O*-acetyl-2-fluoro-*D*-glucal (4)

A mixture of 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-*D*-glucopyranosyl fluoride (1) and trifluoromethyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-*D*-glucoside (2) (1.5g), formed from tri-acetyl-glucal and trifluoromethyl hypofluorite (4) was treated with 30% HBr/HOAc (15 mL) and acetic anhydride (1.5 mL) at room temperature for 6 days. The mixture was poured into ice water and extracted with methylene chloride, and the organic layer washed with saturated sodium bicarbonate. The solution was died, filtered and evaporated. Ether/hexane was added to the residue and the product crystallized to give 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-*D*-glucopyroanosyl bromide (3), (0.87g) m.p. 79-80°. Treatment of (3) with boiling acetonitrile-triethylamine for 1 hr gave the fluoroglucal (4) (0.55g, 44% overall yield) as a syrup after evaporation of the solvent, and extraction with CH_2Cl_2. ^{19}F-NMR data ($CDCl_3$), 188 MHz, external TFA): δ -91.8 (t, $J_{F,1}$ 3.9, $J_{F,3}$ 3.9, F-2).

Synthesis of 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2,2-difluoro-α-*D*-*arabino*-hexopyranose (5)

Acetyl hypofluorite (200 μmol) was prepared as previously described (3) and bubbled through a solution of the glucal (4) (50 mg) at -78° dissolved in Freon-11 ($CFCl_3$). The mixture was evaporated and extracted with dichloromethane and aqueous sodium bicarbonate. The dichloromethane layer was then washed with distilled water, and the organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified on column chromatography using hexane/ethyl acetate (4:1) to afford the 2,2-difluoro-tetra-acetate (48mg, 76%). ^{1}H-nmr data ($CDCl_3$, 200 MHz, external TMS): δ 6.19 (t, 1H, $J_{1,Fe} = J_{1Fa}$ 3.0 Hz, H-1), 5.50 (dt, 1H, $J_{3,Fa}$ 20, $J_{3,Fe} = J_{3,4}$ 10 Hz, H-3), 5.20 (t, 1H, $J_{4,3} = J_{4,5}$ 10Hz, H-4), 4.3 – 4.0 (m, 3H, H-5, H-6, H-6'), 3.88 (s, 3H, OAc, 3.85 (s, 3H, OAc), 3.81 (s, 3H, OAc), 3.74 (s, 3H, OAc). ^{19}F-nmr ($CDCl_3$, 188 MHz, external TFA): δ -44.9 (F-2e, F-2a coincident).

Synthesis of ^{18}F-DFDG (6)

^{18}F-Acetyl hypofluorite was bubbled (120 mL/min) through a solution of the glucal (4) (50mg) at room temperature in $CFCl_3$. After the target gas was emptied the freon was evaporated and HCl (1.5N, 3mL) was added and heated to 120° for 20 minutes. The solution was then passed through a column containing AG11-A8 (3.5 g), Alumina N and C-18 Sep Paks, and finally a sterilizing membrane filter to give the final product in 27% radiochemical yield (approx. 500 mCi/mmol) and 95% chemical and radiochemical purity (tlc). ^{19}F nmr (after decay) (D_2O, 188 MHz, external TFA reference): α-D anomer, F_a –48.5 ($J_{Fa,Fe}$ 251.8), F_e –43.6; β-D anomer, F_a –47.9 ($J_{Fa,Fe}$ 248), F_e – 40.3.

Results and Discussion

[^{18}F]-2-Deoxy-2,2-difluoro-*D*-glucose (DFDG) is readily prepared by treating 3,4,6-tri-*O*-acetyl-2-fluoro-glucal with ^{18}F-acetyl hypofluorite in 27% radiochemical yield (Fig 1). The synthesis was

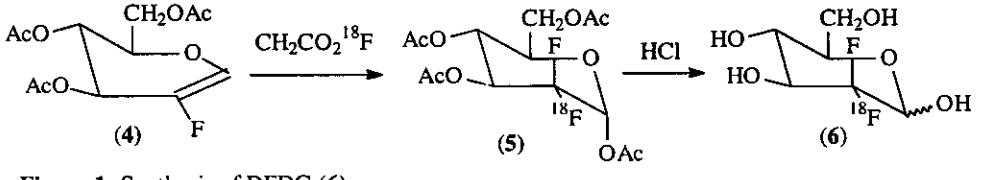

Figure 1: Synthesis of DFDG (6).

conveniently carried out in the same apparatus that is currently used for the synthesis of FDG by the electrophilic fluorination method. Excess glucal (4) decomposes in boiling HCl as does tri-O-acetyl-glucal (TAG). The fluoroglucal (4) was synthesized, as shown in Fig. 3, via the formation of the

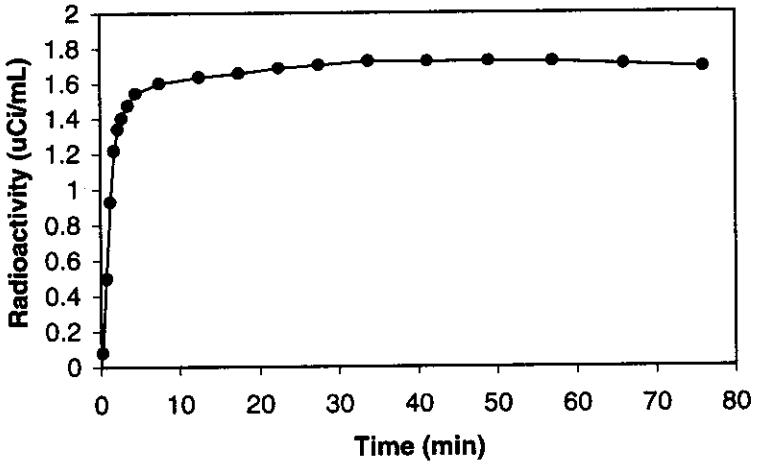

Figure 2. Monkey Brain Uptake Curve

bromo-glycoside (3) from the mixture of fluoro- and trifluoromethyl-glycosides (1,2)(4), followed by elimination with triethylamine (2) to form the 2-fluoro-glucal. The structure of (4) was confirmed by ^{1}H and ^{19}F nmr and the nmr data matched those quoted in the literature. The cold synthesis of the intermediate (5) was carried out in order to confirm the addition of acetyl hypofluorite to the fluoroglucal (4) and to lend support for the structure of DFDG (6). ^{1}H and ^{19}F nmr was consistent with the structure of (5). ^{19}F nmr of a decayed sample confirmed the structure of (6) and was identical to that in the literature (2) for the "cold" compound.

Table 1: Biodistribution of DFDG (%dose/gram)

Organ	15 min	30min	1 h	1.5 h	2 h
Blood	0.47±0.13	1.19±0.13	1.07±0.1	0.53±0.05	0.47±0.12
Brain	1.61±0.17	2.51±0.12	2.95±0.35	1.40±0.08	1.60±0.16
Heart	10.05±2.4	13.88±0.9	6.84±3.35	12.4±0.84	10.0±2.35
Muscle	1.65±0.17	2.67±0.44	1.99±0.35	1.99±0.34	1.65±0.11
Lung	1.06±0.22	2.10±0.3	1.83±0.47	1.89±0.49	1.06±0.22
Liver	0.73±0.14	1.64±0.2	1.52±0.07	0.89±0.04	0.73±0.14

The mouse biodistribution of DFDG reflects that of FDG in that it is rapidly taken up in the heart and remains relatively constant for 2 hours (10% dose/gram) (FDG = 32%, ref. 5). The brain uptake at 2 hours is 1.61% dose/gram as compared to 3.42% for FDG. The heart/lung ratio was 9.46 (FDG = 12) and the heart/liver ratio was 14 (FDG = 32). There is rapid clearance of radioactivity from the blood after injection.

A preliminary brain image of DFDG in a Rhesus monkey showed a similar distribution to that of FDG. The brain uptake data (Fig. 2) from the image show rapid uptake in the brain which remains relatively constant out to 80 minutes. However, the uptake in the surrounding muscle is much higher for DFDG than for FDG.

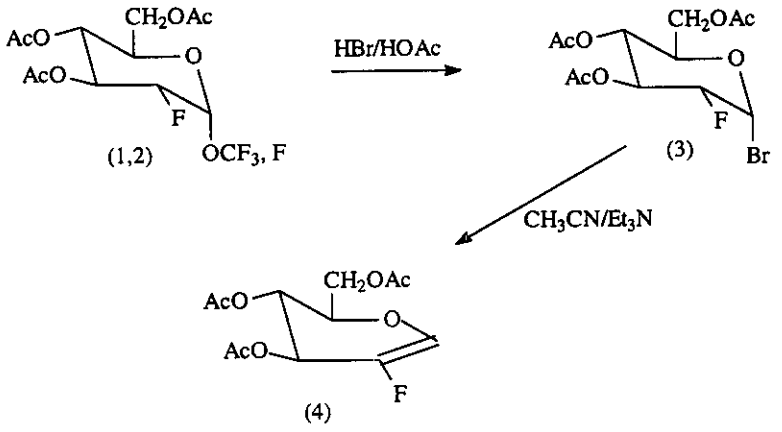

Figure 3: Synthesis of acetylated fluoroglucal (4)

In conclusion DFDG behaves similarily *in-vivo* to FDG but with lower total uptake in the heart and brain.

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