THE EFFECT OF IODINE POSITION ON UPTAKE IN THE MOUSE USING AN ISOMERIC SERIES OF 2-DEOXY-2-O-([^{123}I]-IODOBENZYL)GLUCOSES.

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SUMMARY

The ortho, meta and para iodinated series of 2-deoxy-2-O-(iodobenzyl)glucose (IBG) were prepared by addition of the desired iodobenzyl bromide with 3,4,6-tri-O-acetyl-piperidine-N-D-glucose. Subsequent exchange labelling with [^{123}I]NaI enabled their biodistribution to be studied in mice. The lipophilicity of each compound was measured by their octanol:water partition coefficients, showing the meta- and para-IBG to be more lipophilic than ortho-IBG. Examination of the biodistribution data suggests that there is a correlation between tissue uptake and iodine position(lipophilicity).

Key words: Iodine-123, 2-deoxy-2-O-(iodobenzyl)glucose, biodistribution

INTRODUCTION

Various authors have outlined the cost effectiveness and efficacy of using a glucose analogue in the diagnosing of coronary artery disease and various neurological disorders such as epilepsy, tumors, and Alzheimer's(1-3). Presently, the ß+ emitting ^{18}F-2-deoxy-2-fluoro-D-glucose ([^{18}F]-FDG) is being used as brain and heart imaging agents(4,5). Although these authors mount strong arguments to justify the use of PET for the diagnosis of the above disorders, there is no question that more patients would benefit if a glucose analogue could be labelled with a single photon emitting radionuclide such as ^{123}I.

Many halo-substituted D-glucose derivatives have been reported(6-11), and research has found that modifications of D-glucose should be carried out at the C-2 carbon so as to minimize inhibitions of phosphorylation and transport(12-15). Due to the lability of iodine, 2-deoxy-2-iodo-D-glucose (the closest iodinated analogue to FDG) is too unstable to be of physiological use(11). However, synthesis of 2-deoxy-2-O-(p-iodobenzyl)glucose (4-IBG) by Magata et.

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al.(16) showed that stable 2-substituted iodoglucose analogues could be prepared. The biodistribution of 4-IBG has been studied by Magata using ^{125}I, but the analogous ortho- and meta- iodobenzylglucose analogues have not.

Several authors(17-21) have shown that iodine position on the phenyl ring has an effect on the localization of various radiopharmaceuticals. For this reason, the ortho-, meta- and para-IBG series was studied to determine if the position of the iodine on the phenyl ring affects tissue specificity or blood clearance capabilities of these ether glucoses. Investigators have also found that the effectiveness of certain drugs is effected by their lipophilicity(22-24). We therefore investigated the lipophilic properties, measured by octanol:water partition coefficients, of the isomeric IBG series to determine if there is a correlation between tissue uptake and lipophilicity.

EXPERIMENTAL

Glucose pentaacetate, 4-iodotoluene, 2- and 3-iodobenzyl alcohol, and piperidine were used as supplied by Aldrich Chemical Company Inc. Hydrobromic acid (48% in water) was supplied by BDH Inc. [^{123}I]NaI was used as supplied in 0.05N NaOH by Nordion International Inc. [^{18}F]-FDG was used as supplied by the PET group at TRIUMF. All ^{1}H NMR spectra were recorded with a Varian XL-300 MHz instrument.

Synthetic Procedures

3,4,6-Tri-O-Acetyl-Piperidine-N-D-Glucoside (I)

Compound I was prepared according to the method of J.E. Hodge and C.E. Rist(25). ^{1}H NMR (δ from TMS in $CDCl_3$) 5.173 (t,1H), 4.931 (t,1H), 4.220 (dd,1H), 4.088 (dd,1H), 3.882 (d,1H), 3.701 (d,1H), 3.572-3.640 (m,1H), 2.839-2.933 (m,2H), 2.511-2.634 (m,3H), 2.112 (s,6H), 2.065 (s,3H), 1.550-1.603 (m,6H).

2-Iodobenzylbromide (IIa)

To 2.1g (8.9 mmol) of 2-iodobenzylalcohol was added 2.5 ml (22.0 mmol) of hydrobromic acid (48% in water) and 0.63 ml of concentrated sulphuric acid. The mixture was refluxed for one hour, after which a color change was observed from pale yellow to orange-red. The upper aqueous layer was discarded. The lower layer was recrystallized from chloroform and dried over anhydrous magnesium sulphate to give 2.02g of IIa (76%).

2-Deoxy-2-O-(2'-Iodobenzyl)-3,4,6-Tri-O-Acetyl-Piperidine-N-D-Glucoside(26,27,16)(IIIa)

To a 50 ml RB flask covered with foil, containing 4.10g (10.9 mmol) of glucoside I were added 4.72g of freshly prepared Ag_2O(28), 3.52g of ground drierite and 29 ml of dry benzene under a nitrogen atmosphere. The mixture was stirred for 30 minutes, then cooled to 15°C and 3.85g (12.9 mmol) of IIa was added. The mixture was left to stir for 4 days at which time reaction completion was confirmed by TLC (2:1 Et_2O:toluene). The flask contents were filtered and washed with benzene. Recrystallization from methanol gave 3.0g of IIIa (39%). ^1H NMR (δ from TMS in $CDCl_3$) 1.481-1.590 (m,6H), 1.955 (s,3H), 2.013 (s,3H), 2.065 (s,3H), 2.605-2.705 (m,2H), 2.910-2.985 (m,2H), 3.485-3.760 (m,2H), 4.025-4.125 (m,2H), 4,250 (dd,1H), 4.480 (d,1H), 4.920 (t,1H), 5.040 (d,1H), 5.208 (t,1H), 6.955 (td,1H), 7.296-7.410 (m,2H), 7.798 (d,1H).

2-Deoxy-2-O-(2'-iodobenzyl)glucose (2-IBG)(26)

To 1.0g (1.69 mmol) of IIIa was added 20 ml of 2% sodium methoxide in anhydrous methanol. The solution was left to stir for 30 minutes, then was adjusted to pH 3 using 2N sulphuric acid resulting in the formation of a precipitate. After one hour of refluxing, the mixture was neutralized with barium hydroxide. The mixture was then filtered and washed with a small amount of methanol. The filtrate was rotoevaporated to dryness and triturated with a 15% methanol in chloroform solution to give 0.40g of 2-IBG (59%). 2-IBG was further purified by a Phenomenex 10mm x 250mm C18 HPLC column at a flow rate of 3.0 ml/minute using 50:50 water:methanol. 2-IBG has a retention time of 12.9 minutes. Anal. Calcd.(found) for $C_{13}H_{17}IO_6$: C, 39.41 (39.11); H, 4.32 (4.22). ^1H NMR (δ from TMS in d^6-DMSO for α anomer) 3.053-3.200 (m,2H), 3.425-3.484 (m,1H), 3.542-3.686 (m,3H), 4.386-4.424 (t,1H), 4.528-4.694 (m,2H α and ß), 4.906 (d,1H), 4.954 (d,1H), 5.150 (t,1H), 6.370 (d,1H), 7.037 (t,1H), 7.396 (t,1H), 7.585 (d,1H), 7.816 (d,1H). 2-IBG exists as 75:25, α:ß anomers in d^6-DMSO shortly after sample preparation.

3-Iodobenzylbromide (IIb)

Compound IIb was prepared by the same method as for IIa, having 87% yield.

2-Deoxy-2-O-(3'-Iodobenzyl)-3,4,6-Tri-O-Acetyl-Piperidine-N-D-Glucoside(26,27,16)(IIIb)

Prepared by the same method as for compound IIIa using 2.11g (5.6 mmol) of glucoside I,

2.43g of freshly prepared Ag_2O(28), 1.81g of ground drierite, 15 ml of dry benzene and 1.98g (6.6 mmol) of IIb. Recrystallization from methanol gave 1.2g of IIIb (36%). ^1H NMR (δ from TMS in $CDCl_3$) 1.518-1.550 (m,6H), 2.005 (s,3H), 2.020 (s,3H), 2.065 (s,3H), 2.615-2.705 (m,2H), 2.860-2.955 (m,2H), 3.490-3.655 (m,2H), 3.985-4.100 (m,2H), 4.215 (dd,1H), 4.550 (d,1H), 4.785-4.940 (m,2H), 5.145 (t,1H), 7.055 (t,1H), 7.225 (d,1H), 7.608 (d,1H), 7.660 (s,1H).

2-Deoxy-2-O-(3'-iodobenzyl)glucose (3-IBG)

Compound IIIb was deprotected by the same method used for the deprotection of 2-IBG. 3-IBG was further purified by a Phenomenex 10mm x 250mm C18 HPLC column at a flow rate of 3.0 ml/minute using 50:50 water:methanol. 3-IBG has a retention time of 14.4 minutes, giving 0.30g of HPLC pure 3-IBG (40%). Anal. Calcd.(found) for $C_{13}H_{17}IO_6$: C, 39.41 (39.27); H, 4.32 (4.21). ^1H NMR (δ from TMS in d^6-DMSO for the α anomer) 3.060-3.102 (m,2H), 3.404-3.476 (m,1H), 3.524-3.631 (m,3H), 4.389 (t,1H), 4.596 (s,2H), 4.887 (d,1H), 4.942 (d,1H), 5.106 (t,1H), 6.327 (d,1H), 7.370 (d,1H), 7.131 (t,1H), 7.620 (d,1H), 7.768 (s,1H). 3-IBG exists as 85:15, α:ß anomers in d^6-DMSO shortly after sample preparation.

4-Iodobenzylbromide (IIc)

Compound IIc was prepared by the bromination of p-iodotoluene as described by the method of H.A. Sloviter(29).

2-Deoxy-2-O-(4'-Iodobenzyl)-3,4,6-Tri-O-Acetyl-Piperidine-N-D-Glucoside(26,27,16)(IIIc)

Compound IIIc was prepared by the same method used for compound IIIa using 2.0g (5.36 mmol) of glucoside I, 2.0g of freshly prepared Ag_2O(28), 1.5g of ground drierite, 14 ml of dry benzene and 1.93g (6.5 mmol) of IIc. The mixture was left to stir for 7 days at which time reaction completion was confirmed by TLC (2:1 Et_2O:toluene). The flask contents were filtered and washed with benzene. Recrystallization from methanol (3 ml/g) gave 2.04g of IIIc (64%). A second recrystallization was performed using di-isopropyl ether (15 ml/g) which gave an analytically pure product. Anal. Calcd.(found) for $C_{24}H_{32}INO_8$: C, 48.90 (49.01); H, 5.47 (5.42); N, 2.38 (2.35). mp 105-106 °C.

2-Deoxy-2-O-(4'-iodobenzyl)glucose (4-IBG)

Compound IIIc (0.887g) was deprotected by the same method used for the deprotection of IIIa. The crude solid was then recrystallized twice from methanol giving 0.146g of 4-IBG (25%). An additional recrystallization from 99% ethanol yielded analytically pure 4-IBG. Using a Waters C18 μBondapak 4.6mm x 250mm column with 50:50:.5 methanol:water:acetic acid at a flow rate of 1.0 ml/minute, 4-IBG has a retention time of 11.1 minutes. Anal. Calcd.(found) for $C_{13}H_{17}IO_6$: C, 39.41 (39.67); H, 4.32 (4.40); I, 32.04 (31.96). mp 172-173 °C. ^{1}H NMR (δ from TMS in d^6-DMSO for the α anomer) 3.020-3.098 (m,2H), 3.392-3.467 (m,1H), 3.514-3.625 (m,3H), 4.274 (t,1H), 4.679 (d,2H), 4.883 (t,1H), 4.080 (t,1H), 5.106 (t,1H), 6.299 (d,1H), 7.191 (d,2H), 7.688 (d,2H). 4-IBG exists as 99:1, α:ß anomers in d^6-DMSO shortly after sample preparation.

Octanol:water Partition Coefficients

Octanol:water partition coefficients were performed by the shake-flask method(30,31) and measured by UV detection. The samples were extracted using 1:1 volumes of octanol:water (where the water contains 0.05M Trizma buffer pH 7.4 and 0.15M NaCl) at approximately 0.1 mM sample concentrations. The mean log P values are reported herein.

Labelling of 2-, 3-, and 4-IBG

Labelling of the glucose analogues were carried out by the kit type method of Dougan et. al.(32), resulting in 97% radiolabelling yield. Radiochemical purity and stability were determined by SiO_2 TLC (using 30% methanol in chloroform) and RP HPLC (using 50:50 methanol:water).

Biodistribution Studies

Biodistribution studies were carried out using male CDI/UBC mice (20-25g). Animals were injected with 37 KBq (1 μCi) of ^{123}I-glucose analogue or 25 μCi of [^{18}F]-FDG and sacrificed at 15, 30, 60, 180 or 1080 minutes post injection. The activity in the blood, liver, kidneys, spleen, pancreas, stomach, lung, heart, muscle and brain were determined and results expressed as % injected dose per gram of tissue.

DISCUSSION

Preparation of viable 2-substituted glucose analogues labelled with ^{123}I inherently requires that the iodine be stabilized by an unsaturated group(15,16). Although this introduces a bulky substituent in the glucose molecule, Magata's brain uptake studies show indications of [^{125}I]-4-IBG competing for the glucose carrier transport site. We prepared the complete iodinated series of 2-deoxy-2-O-(iodobenzyl)glucoses (i.e. 2-, 3- and 4-IBG) as shown in figure 1, according primarily to the Berry and Dutton(26) synthesis of 2-deoxy-2-O-(benzyl)glucose, while using the quantities and longer reaction times reported by Magata(16). All analogues showed in vitro stability after 48 hours.

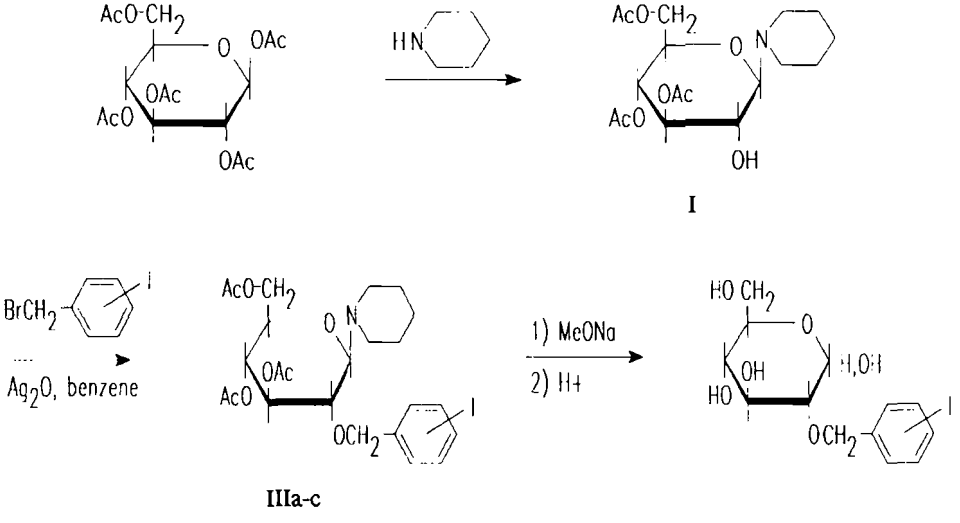

Figure 1. Synthesis of 2-, 3- or 4-IBG.

The mice biodistribution studies of the 2-deoxy-2-O-(iodobenzyl)glucose analogues showed that the overall tissue uptake was too low for these analogues to be used as heart or brain imaging agents. However, although tissue uptake was not high, some general trends were observed for the isomeric 2-deoxy-2-O-(iodobenzyl)glucose analogues. For time periods up to 60 minutes, [^{123}I]-4-IBG has the greatest heart uptake followed by [^{123}I]-3-IBG and finally [^{123}I]-2-IBG. This is the general trend for all organs, with the exception of the liver, kidney, and stomach which show no preferential uptake for a specific isomer. At 180 minutes post injection, all organs except the brain show [^{123}I]-2-IBG to have the lowest tissue uptake while [^{123}I]-3- and 4-IBG have statistically the same tissue uptake. Magata's work has shown that [^{123}I]-4-IBG does not undergo phosphorylation by hexokinase. One would therefore not expect heart:blood

ratios to be greater than one. We found this to be true for all analogues except [^{123}I]-4-IBG which has a heart:blood ratio of 1.24 ± 0.08 at 15 minutes post injection. It is interesting to note that Magata also reports a heart:blood ration of 1.09 at 20 minutes post injection. All of the IBG analogues, however, appear to slowly wash out of the heart with no indication of accumulation (see Tables 1-3).

Table 1. Biodistribution Data for [^{123}I]-2-IBG.

	15min.	30min.	60min.	180min.	1080min.
Blood	3.23±0.41	1.63±0.46	0.68±0.20	0.05±0.01	0.005±0.001
Liver	7.00±0.57	3.55±1.16	2.34±0.24	0.09±0.01	0.01±0.002
Kidney	7.35±0.95	5.78±2.78	3.96±0.68	0.26±0.05	0.01±0.001
Spleen	2.17±0.31	1.00±0.44	0.25±0.07	0.02±0.007	-
Pancreas	4.28±2.48	1.45±0.52	0.52±0.15	0.01±0.001	-
Stomach	5.37±2.92	2.15±0.90	1.28±0.87	0.10±0.04	0.002±0.001
Lung	3.05±0.31	1.47±0.44	0.59±0.13	0.05±0.001	0.003±0.001
Heart	2.76±0.45	1.06±0.32	0.27±0.08	0.01±0.005	-
Muscle	2.31±0.33	1.07±0.32	0.33±0.10	0.008±0.005	-
Brain	0.22±0.02	0.16±0.01	0.10±0.02	0.03±0.004	-

Table 2. Biodistribution Data for [^{123}I]-3-IBG.

	15min.	30min.	60min.	180min.	1080min.
Blood	3.50±0.23	3.14±0.44	1.27±0.21	0.53±0.05	0.03±0.002
Liver	5.57±0.27	5.38±0.77	2.25±0.43	0.77±0.10	0.04±0.007
Kidney	7.22±0.54	5.82±0.68	2.64±0.47	1.07±0.08	0.03±0.006
Spleen	2.45±0.17	2.09±0.28	0.86±0.17	0.30±0.01	0.01±0.007
Pancreas	3.35±0.30	2.87±0.34	1.18±0.22	0.44±0.04	-
Stomach	2.66±0.14	2.39±0.48	1.12±0.10	0.43±0.09	0.02±0.01
Lung	3.25±0.20	2.73±0.33	1.21±0.14	0.46±0.03	0.04±0.005
Heart	3.25±0.27	2.84±0.36	1.12±0.23	0.40±0.03	0.001±0.001
Muscle	2.10±0.20	1.88±0.21	0.88±0.14	0.35±0.05	-
Brain	0.25±0.04	0.22±0.02	0.19±0.02	0.14±0.01	0.005±0.002

Table 3. Biodistribution Data for [^{123}I]-4-IBG.

	15min.	30min.	60min.	180min.	1080min.
Blood	4.80±0.14	4.49±0.71	2.56±0.28	0.67±0.25	0.23±0.03
Liver	6.96±0.47	5.62±1.05	3.73±0.93	0.87±0.36	0.41±0.09
Kidney	8.51±0.34	8.31±1.29	4.64±0.41	1.23±0.45	0.25±0.04
Spleen	3.56±0.13	3.16±0.45	1.75±0.24	0.47±0.19	0.20±0.05
Pancreas	4.50±0.22	3.86±0.60	2.24±0.38	0.57±0.22	0.05±0.02
Stomach	3.42±0.55	3.28±0.72	2.48±0.24	0.92±0.43	0.15±0.04
Lung	4.71±0.44	4.19±0.56	2.21±0.39	0.59±0.26	0.14±0.03
Heart	5.95±0.40	5.15±0.53	2.81±0.40	0.66±0.24	0.08±0.02
Muscle	2.55±0.23	2.67±0.43	1.64±0.18	0.37±0.15	0.38±0.04
Brain	0.24±0.02	0.29±0.45	0.41±0.36	0.24±0.07	0.10±0.01

The brain uptake for [^{123}I]-4-IBG remains constant for 160 minutes, while [^{123}I]-3-IBG has a constant brain uptake for only 45 minutes, and the brain uptake for [^{123}I]-2-IBG slowly decreases after 15 minutes post injection. Although Magata found [^{123}I]-4-IBG to be a promising brain imaging agent, when one examines the brain:blood ratios, they are 0.60 ± 0.19, 0.26 ± 0.06, and 0.36 ± 0.28 for [^{123}I]-2-, 3-, and 4-IBG respectively at 180 minutes post injection. [^{123}I]-2-IBG has a high brain:blood ratio due to its more efficient blood clearance, rather than a high overall uptake. These ratios are comparable with that found for the transport tracer 3-[^{11}C]-methyl-D-glucose(33).

The study of this series of analogues has also shown that iodine position effects the lipophilicity of these compounds. The log of the octanol:water partition coefficients for 2-, 3-, and 4-IBG are 0.44 ± 0.01, 0.61 ± 0.03, and 0.66 ± 0.03 respectively. Differences in lipophilicities are reflected in differences in tissue uptake. The differences in lipophilicity effect the efficiency of blood clearance as well as the tissue uptake. Although [^{123}I]-2-IBG has the lowest tissue uptake, it has the most efficient blood clearance, presumably due to its relative hydrophilic nature. These observed differences in tissue uptake may therefore be due to 1) a particular iodine position being favored for optimal binding interactions with glucose transport proteins, 2) different lipophilicities influencing pore mediation efficiency or most likely 3) a combination of both effects 1 and 2. More studies, however, are necessary to elucidate the reasons for the observed biodistribution data.

For comparison, biodistribution studies for [^{18}F]-FDG were also carried out in mice at the same time periods used for the IBG analogues (see Table 4). These results were interesting in themselves since other investigators rarely examine time periods greater than 180 minutes post injection when using [^{18}F]-FDG. The heart uptake for[^{18}F]-FDG is 47.37% dose/g and increases to 93.91% dose/g from 15 to 180 minutes post injection. At 1080 minutes post injection, the heart uptake has significantly decreased to 9.26% dose/g. The brain uptake is 7.37% dose/g and increases to 12.77% dose/g from 15 to 60 minutes post injection. At 1080 minutes post injection the brain uptake has also decreased to 0.14% dose/g. These results show that [^{18}F]-FDG is not permanently "trapped" in the brain or heart tissues. The best IBG analogue, [^{123}I]-4-IBG, has a maximum brain and heart uptake of only 0.41% dose/g (at 60

Table 4. Biodistribution Data for [^{18}F]-FDG.

	15 min.	30 min.	60 min.	180 min.	1080 min.
Blood	1.82±0.10	0.91±0.10	1.06±0.12	0.94±0.12	0.01±0.007
Liver	2.31±0.15	1.43±0.24	2.23±0.39	2.81±0.33	0.16±0.12
Kidney	3.42±0.40	2.87±0.98	3.11±0.66	2.51±0.33	0.08±0.27
Spleen	2.88±0.21	2.33±0.43	4.23±0.62	4.77±0.89	0.16±0.09
Pancreas	3.39±0.25	3.44±0.61	5.02±0.57	6.26±0.58	-
Stomach	7.59±0.90	4.96±1.22	7.70±2.11	10.01±2.07	0.49±0.16
Lung	4.11±0.79	3.84±0.78	5.55±1.18	6.47±1.18	0.65±0.52
Heart	47.37±10.37	56.03±18.61	70.38±18.97	93.91±17.03	9.26±3.87
Muscle	5.17±1.05	6.82±1.29	7.86±2.77	10.35±2.57	1.06±0.73
Brain	7.37±1.44	8.74±1.70	12.77±1.65	8.39±1.79	0.14±0.16

minutes post injection) and 5.95% dose/g (at 15 minutes post injection) respectively.

It appears that even for nonmetabolized analogues such as the IBG series, tissue uptake differences between isomers are still observed. As one can see, FDG is far superior to any of the IBG ether glucose derivatives studied. Future work will therefore attempt to answer the question of preferential uptake of iodinated isomers as well as the continual search for other glucose analogues that may show greater specific tissue uptake.

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