Metabolic Trapping as a Principle of Radiopharmaceutical Design: Some Factors Responsible for the Biodistribution of [^{18}F] 2-Deoxy-2-Fluoro-D-Glucose

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Initially, [^{18}F]2-deoxy-2-fluoro-D-glucose (F-18-DG) distributes to the kidneys, heart, brain, lungs, and liver of the mouse, and clears rapidly from all except the heart and, to a much lesser extent, the brain. The heart and brain showed the highest rates of phosphorylation both in vivo and in vitro. No detectable glucose-6-phosphatase activity was present in these organs when hexokinase activity was high and at pH 6.5. The rank order for hexokinase activity, measured in vitro, was brain > heart ≃ kidney > lung > liver, whereas glucose-6-phosphatase activity was found only in the liver and to a lesser extent in the kidney, at pH 6.5. The rate of appearance of F-18-DG-6 phosphate (F-18-DG-6-P) in vivo was significantly slower in the lungs, liver, and kidneys than in the heart and brain, and represented a small proportion of the initial radioactivity. The F-18-DG that clears from the organs is excreted into the urine mostly unchanged, apparently due to the lack of tubular resorption. The rapid excretion of F-18-DG from liver, lungs and kidneys, and the retention by the heart and brain, is the result of metabolic trapping within certain organs and is reflective of glucose utilization. These results may contribute to the clinical utility of F-18-DG by providing a basis for metabolic studies in vivo. Metabolic trapping can be considered as a principle in the design of radiopharmaceuticals as metabolic probes for function or tumor location.

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The success of a radiopharmaceutical depends, to a large extent, upon its ability to preferentially concentrate within the target tissue. The factors responsible for the tissue specificity of a radiopharmaceutical are not well understood, in general, and no doubt vary from one class of compounds to another. An understanding of the phenomena governing the disposition of successful radiopharmaceuticals is useful both for the design of new tracers and in defining the limits of clinical interpretation that can be expected from imaging studies.

[^{18}F] 2-deoxy-2-fluoro-D-glucose (F-18-DG) has been shown to be a useful radiopharmaceutical for the quantitative determination of regional brain glucose metabolism, and it also localizes in the heart (*1,2*). The choice of F-18-DG as a radiopharmaceutical for measuring local glucose metabolism was based on a series of observations that began with studies on carbohydrate metabolism in 1954 by Sols and Crane (*3*). They reported that the use of 2-deoxy-D-glucose (an analog of D-glucose in which the hydroxyl group at C-2 was replaced by hydrogen atom) as a substrate for the enzyme hexokinase "isolates the hexokinase reaction" in that the hexose phosphate formed is metabolically trapped and does not enter into the subsequent metabolic steps of glycolysis. This property has been extremely useful and 2-deoxy-D-glucose has been exploited as a sub-

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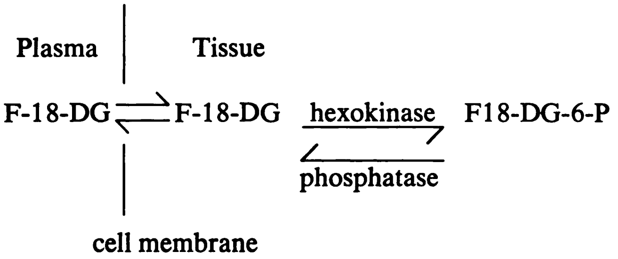
strate in probing many aspects of carbohydrate metabolism. Sokoloff, Reivich, and their coworkers (*4*) used these properties of 2-deoxy-D-glucose in the development of an elegant method for the simultaneous measurement of the rates of glucose consumption in the various structural and functional components of brain in vivo using [^{14}C] 2-deoxy-glucose and quantitative autoradiography. An extension of this method utilizing a suitably labeled 2-deoxy-D-glucose analog might allow the measurement of local brain glucose metabolism in man using emission tomography (*5,6*). This requires that 2-deoxy-D-glucose be labeled with a gamma or positron-emitting nuclide that would not significantly alter its biochemical characteristics. The use of F-18 as a label at C-2 was chosen since a) the hexokinase reaction is relatively insensitive to structural modification at this position (*7*), b) the C–F bond is strong, resulting in stability of the label; and c) the characteristics of F-18 for positron emission tomography, for radiopharmaceutical synthesis, and for patient dosimetry are nearly ideal. Furthermore, it is known that F-DG is a suitable substrate for hexokinase (*8*) and that 2-deoxy-2-fluoro-D-glucose-6-phosphate (F-18-DG-6-P) is a relatively poor substrate for subsequent metabolic steps (*9*). While some hexoses can readily be transported across cell membranes, the membrane permeability to hexose phosphates, the immediate enzymatic products, is quite low (*10*). Thus the retention, or perhaps the clearance, of radioactivity may be dependent upon the relative rates of the subsequent reactions or transport processes within a given tissue.



Previous studies (2) have shown that after i.v. administration of F-18-DG the radioactivity distributes rather uniformly and then clears rapidly from all organs except the brain and heart, where it remains essentially constant in the heart for at least 2 hr and decreases slowly, between 1 and 2 hr, in the brain. In mice, dogs, and man, the activity that clears from the other organs is excreted to a large extent into the urine. The mechanism that determines whether the activity is retained or lost from an organ has not been demonstrated experimentally. This study was undertaken to learn whether the chemical forms of the radioactivity present in various tissues and excreted into the urine are in accord with metabolic trapping, and to determine to what extent the observed organ clearances could be correlated with the glycolytic enzyme activities of these tissues.

METHODS

Radiopharmaceutical synthesis. [^{18}F] 2-deoxy-2-fluoro-D-glucose (F-18-DG) was prepared as previously described (*2,11,12*). Typical specific activities used in these experiments were 0.3–1.0 mCi/mg (end of synthesis). The radiochemical purity of the product was typically 96–98% with a 2–4% unidentified radiochemical impurity. The radiochemical purity was assayed by TLC using silica gel G and $CHCl_3$:CH_3OH:H_2O (30:9:1). In this system the FDG and radioactive impurity had R_f values of = 0.25 and 0.7, respectively. Gas chromatography and radioactivity assays of the trimethylsilyl derivative of the product using the general method described by Sweeley and coworkers (*13*) (conditions described below) showed essentially all of the activity to be congruent with the mass peaks (Figure 3a) corresponding to the 2 anomers and a trace of a third form of F-DG (retention times 9.77, 12.41 and 16.31 min) and a 2–4% impurity with a shorter retention time (4.5 min).

[^{18}F] 2-deoxy-2-fluoro-D-glucose-6-phosphate (F-18-DG-6-P) was synthesized enzymatically in a modification of a procedure described by Bessell and coworkers (*14*). F-18-DG was added to a 3-ml reaction mixture containing 5 millimolar ATP, 5 millimolar $MgCl_2$, and 40 millimolar potassium phosphate buffer at pH 7.6. Reactions were carried out for 45 min at 33°C and terminated with 3 ml 0.4 M $HClO_4$. The mixture was centrifuged at 2000 g for 5 min, the supernatant was adjusted to pH 7.5 with KOH and then applied to a 1- × 4-cm column of AG1X8 ($CO_3^=$ form) and washed with 100 ml water. The F-18-DG-6-P was eluted with 60 ml of 0.5 N HCl and evaporated under reduced pressure at 35°C. The F-18-DG-6-P was redissolved in distilled water for use in the enzyme studies. The radiochemical purity of the F-18-DG-6-P was checked by thin layer chromatography on silica gel G with ethanol:ethyl acetate (1:1, $R_f = 0.2$). Recovery was by rechromatography on AG1X8 columns and was typically > 98%.

F-18-DG metabolite studies. Swiss albino mice (BNL strain), maintained on a standard rodent diet and water *ad libitum*, were injected intravenously through a lateral tail vein with F-18-DG dissolved in isotonic saline and killed at the desired time by cervical dislocation. The organs to be studied were removed as quickly as possible, blotted to minimize adhering blood, and a small piece of the tissue was immediately homogenized in a ground-glass homogenizer containing 5 ml of 0.4 M $HClO_4$. An additional piece of each tissue was placed in a tared counting vial and its radioactivity determined in an automated NaI well counter to determine the percentage of the injected dose per gram of tissue. Three milliliters of homogenate were transferred to glass centrifuge tubes specifically constructed to fit into a well counter and the total radioactivity in the sample determined. The homogenates were centrifuged at 2000 g for 5 min to remove the denatured protein; the supernatants were then decanted and both the pellets and the supernatants were counted for radioactivity. The difference between the total homogenate radioactivity and that in the supernatant was used to calculate an extraction efficiency (typically 95%). The pH of each supernatant was then adjusted to ~7.5 with solid $KHCO_3$ and applied to a 1- × 4-cm column of AG1X8 ($CO_3^=$ form) seated in a vacuum manifold. The free F-18-DG was separated from the F-18-labeled anionic products by washing the column with 100 ml of water under slightly reduced pressure. The volumes of the water washes were recorded and 5-ml aliquots were removed and counted for radioactivity. The resins were also counted for radioactivity. The recoveries throughout these procedures ranged from 85 to 106% ($n = 100$). Data are expressed as the mean from separate determinations on four individual animals at each point for each tissue. The percentage of F-18-DG-6-P was calculated from the radioactivity remaining on the resin, compared with the radioactivity in the original homogenate supernatant, assuming that the F-18-DG is eluted in the water. The validity of this method was confirmed by the addition of known amounts of F-18-DG, F-18-DG-6-P, or both compounds to tissue samples and carrying out the above procedure. F-18-DG-6-P breakthrough was <5% and F-18-DG recovery >95%.

Analysis of radioactivity in urine. In duplicate experiments, two mice were injected with 50–100 μCi each of F-18-DG, and urine was collected for 90 min. The chemical form of the radioactivity in the urine was determined by gas chromatography and radioactivity assays, thin layer chromatography, and anion-exchange chromatography both before and after reaction with hexokinase. Free fluoride was assayed by lead precipitation and by filtration through alumina (*2*).

Gas chromatography and radioassay of eluants. An aliquot of urine (25 μl) was added to carrier F-DG (0.87 mg) that had been converted to an equilibrium mixture of anomers by heating at 90° for 10 min with 0.1 ml of water. The solution was evaporated to dryness and 0.1 ml of dry pyridine, 25 μl of hexamethyldisilazan, and 10 μl of chlorotrimethylsilane added. After 10 min at room temperature, 15 μl (50,000–100,000 dpm) of this mixture was assayed by gas chromatography (*12*). Radioactivity was assayed by collecting 1-min fractions from the exit port of the thermal-conductivity detector and counting in a well counter. Recovery of injected radioactivity ranged from 75 to 90%. Analyses were performed on a gas chromatograph* using a DC 710 column (10 ft × ¼ in., 10% on chromosorb W) with column temperature 190° and flow rate 98 ml/min. Retention times for the two silylated anomers of 2-deoxy-2-fluoro-D-glucose are 9.8 and 12.4 min. A minor component—possibly a "γ" sugar at 16.31 min—was also present.

Thin-layer chromatography. Urine was chromatographed with carrier F-DG (silica gel G, ethanol: ethyl acetate (1:1). Radioactivity was assayed by sectioning the chromatogram and counting the sections in a well counter. F-DG was detected with I_2 and had $R_f = 0.67$ in this system

Reaction with hexokinase. An aliquot of urine was incubated with a 3-ml reaction mixture containing 5 millimolar ATP, 5 millimolar $MgCl_2$, 40 millimolar KCl and 6 I.U. hexokinase† in 40 millimolar potassium phosphate buffer (pH 7.6) at 33°C for 60 min. This solution was applied to a AG1X8 ($CO_3^=$) column (1 × 4 cm) and eluted with water (9 fractions of 8 ml each). The water fractions and resin were counted in a well counter. In an additional experiment, urine was subjected to the identical ion-exchange analysis without incubation with hexokinase.

Fluoride analysis. Free fluoride was assayed by passing urine through an alumina column and by PbFCl precipitation as previously described (*2*).

Determination of hexokinase and phosphatase activities of tissues in vitro. Homogenates of lung, liver, brain, heart, and kidney were prepared using a Potter-Elvehjem homogenizer and 0.25 *M* sucrose at 0° in 0.1 *M* potassium phosphate buffer, pH = 7.6. The homogenates were centrifuged at 600 g twice and the supernatants analyzed for protein concentration by the method of Lowry (*15*), with bovine serum albumin as a standard. Homogenates were diluted to the appropriate concentration with the above buffer and stored at −20°C until used for enzyme studies. No detectable loss of enzyme activity was observed after storage for several weeks.

Hexokinase activity was measured in the homogenates in 1-ml reaction mixtures containing an aliquot of the tissue homogenate (50 μg–7 mg protein/ml) and 2–100 μ*M* F-18-DG, 5 millimolar ATP, 5 millimolar $MgCl_2$, 40 millimolar KCl, 40 millimolar potassium phosphate buffer at pH 7.6. Reactions were carried out at 33°C and were terminated at the

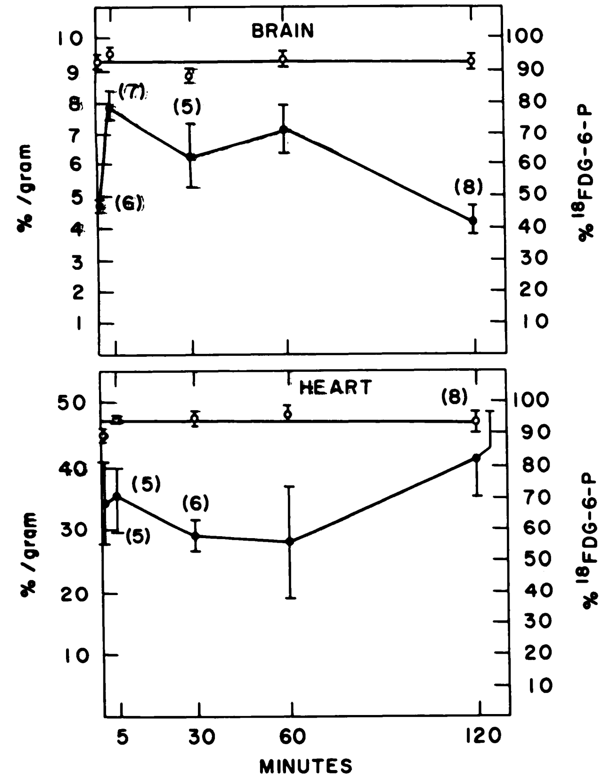


FIG. 1. Distribution, in mouse brain and heart, of F-18 radioactivity (●—● expressed as % of injected dose per gram) and F-18-DG-6-P) (○—○ expressed as % of total tissue activity contributed by F-18-DG-6-P). Each point represents the mean from four to eight animals as indicated ± sdm.

desired time by addition of 1 ml 0.4 *M* $HClO_4$ at 0°. The reaction mixture was centrifuged for 5 min at 2000 g to remove the protein, and the supernatant was adjusted to pH 7.5 with KOH solution. Aliquots (100 μl) of this solution were applied in duplicate to AG1X8 columns (0.5 × 2.5 cm) and the free F-18-DG eluted from the column with 6 ml water. The F-18-DG eluted from the column was counted for radioactivity. Identical aliquots of each solution to be applied to the columns were taken for counting standards, and the difference between this activity and the water wash was used to calculate the % F-18-DG-6-P in the sample. Recovery of radioactivity by this method was typically $> 94\%$.

Glucose-6-phosphatase activity was measured in two ways. First, since the presence of phosphatase activity in the homogenates could conceivably alter the measurement of hexokinase activity, the reverse reactions were performed using the identical conditions described above except that F-18-DG-6-P was used as the substrate. Second, since the pH optimum for glucose-6-phosphatase is ~6.5 (*16*), reverse reactions were also carried out in 1 ml 50-millimolar cacodylate buffer (pH 6.5), with F-18-DG-6-P and an appropriate dilution of tissue homogenate. The reaction mixtures were analyzed as described above.

RESULTS

The relative amounts of F-18-DG and F-18-DG-6-P in brain, heart, liver, kidneys and lungs, as well as the percentage of injected dose/gram (determined on the same tissue samples) were determined in mice at 1, 5, 30, 60, and 120 min after injection. These data are illustrated in Figs. 1 and 2. Briefly, the heart showed a high and relatively constant amount of radioactivity over the time course of the study, and also showed that the chemical form of the F-18 activity in these organs was as F-18-DG-6-P (Fig. 1). In contrast, in the lungs, liver, and kidneys, all of which showed a rapid clearance of radioactivity, the chemical form of the F-18 was largely as unmetabolized F-18-DG in the early stages (Fig. 2). Later the F-18-DG-6-P became predominant, although its actual concentration remained constant

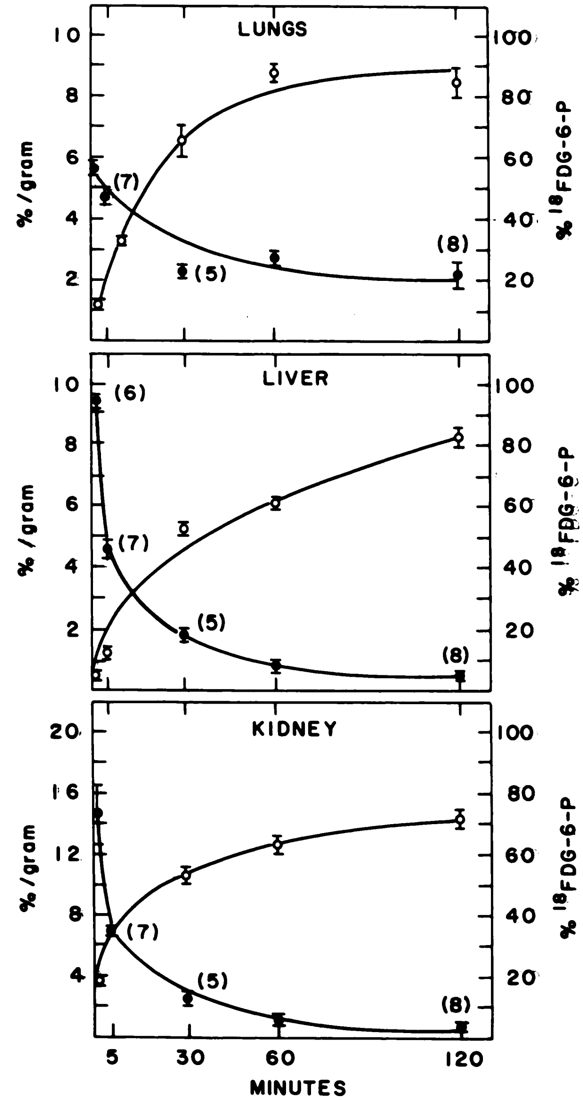


FIG. 2. Distribution, in mouse lungs, liver and kidney, of F-18 radioactivity (●—●) and F-18-DG-6-P (○—○) each expressed as in Fig. 1. Each point represents the mean from four to eight animals as indicated ± sdm.

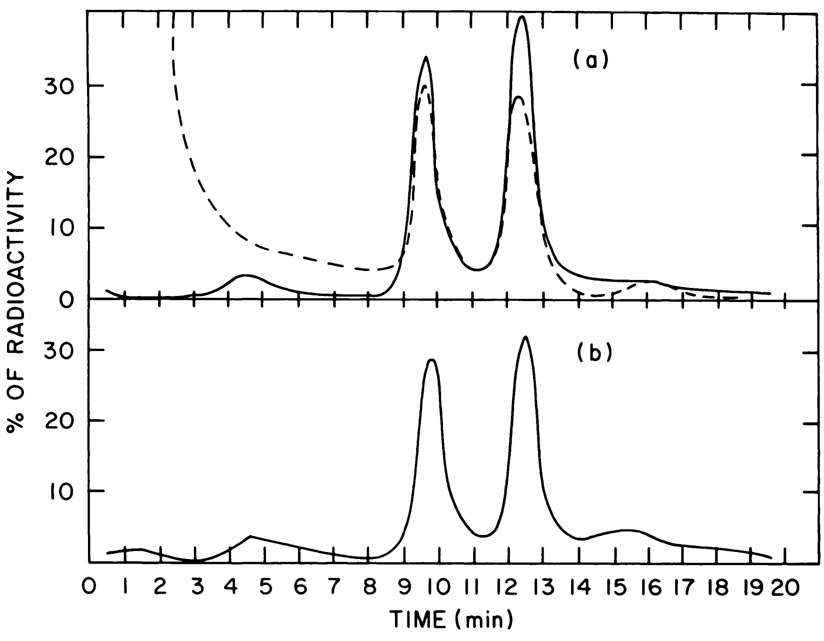


FIG. 3. (a) Gas-chromatographic analysis of trimethylsilyl derivative of F-18-DG (anomeric mixture) showing mass profile (- - - -) with corresponding radioactivity profile (———). (b) Radioactivity profile of gas-chromatographic analysis of trimethylsilyl derivative of mouse urine collected during the first 90 min after injection. Column conditions in (a) and (b) were identical.

because of the rapid clearance of the total radioactivity.

Although the brain does show a decreased F-18 radioactivity at 2 compared to 1 hr, the fact that virtually all of the activity from 1 min to 2 hr was present as F-18-DG-6-phosphate supports the concept of metabolic trapping (Fig. 1). This trapping is certainly not irreversible, only the back reaction is relatively slow compared to liver, kidneys, and lungs. If the time required for measurement of brain activity is relatively fast compared to the brain loss of activity (confirmed by unpublished data), then the activity can be considered to be trapped over this time scale. The 60- and 120-min heart activities are not significantly different. We have consistently experienced relatively large variations in heart activities at several time intervals, the reason for which is unknown but may relate to the physiological state of the animal at the time of injection.

The mice excreted 15–25% of the injected radioactivity in 90 min. The predominant chemical form of the radioactivity (>90%) was determined to be unchanged F-18-DG using gas chromatography and radioactivity assay on the trimethylsilyl (TMS) derivative of urine to which carrier F-DG was added (Fig. 3), as well as thin-layer chromatography. The latter showed that ~4% of the radioactivity was not F-18-DG. The urinary radioactivity was shown to be a substrate for hexokinase by incubation of a urine sample with hexokinase to produce the anionic metabolite, F-18-DG-6-P. When a sample of unreacted urine was subjected to anion-exchange chromatography, ~5% appeared to be anionic. On passage of an aliquot of the urine through an alumina column that we have previously shown to retain fluoride quantitatively (*2*), 5% was retained. The addition of carrier fluoride ion to the urine, followed by precipitation as PbFCl, showed that less than 1.3% of the radioactivity could possibly be fluoride or some metabolite behaving like fluoride. Thus it appears that the alumina column also partially retains some unidentified metabolite and, possibly, fluoride ion.

Homogenates of brain, heart, lungs, liver, and kidneys were incubated with F-18-DG and F-18-DG-6-P in order to determine their relative hexokinase and phosphatase activities. The results (Fig. 4) showed that the brain had the highest hexokinase activity (nmol F-18-DG phosphorylated per milligram protein per minute) followed by heart and kidney, which had approximately equal enzyme activity. The lungs had considerably higher hexokinase activity than the liver, which had the lowest hexokinase activity of the tissues studied. The same organs were incubated with F-18-DG-6-P to determine the extent to which the phosphatase activity catalyzed conversion to F-18-DG. Phosphatase activity could not be detected at pH 7.6 in any of these tissues, and at pH 6.5 only the liver showed significant phosphatase activity (Fig. 5) although kidney also demonstrated a slight phosphatase activity.

DISCUSSION

Initial tissue distribution studies using F-18-DG revealed that the substitution of a fluorine atom for a hydroxyl group at C-2 on glucose resulted in some striking and useful biodistribution patterns, namely a high uptake in the heart and brain, rapid clearance from lungs, liver, and kidneys, and a rapid excretion of radioactivity into the urine (2).

Perhaps the most obvious difference in the behavior of F-18-DG when one compares it with glucose, is its excretion into the urine. Blood levels of glucose are maintained relatively constant through the resorption of glucose by the renal proximal tubule cells. This resorption process has been shown to be an active transport, depending upon the interaction of glucose with a receptor in the luminal brush-border membrane of the proximal-tubule cells. Silverman and coworkers have studied the structural requirements for the resorption of simple sugars by both dog and human kidney (*17,18*) and have shown that 2-deoxy-glucose, a structurally similar analog of F-18-DG, has a very low affinity for the glucose receptor, thus demonstrating the importance of a hydroxyl group at C-2 for renal resorption.

Our observation that F-18-DG is excreted essentially unchanged further refines the structural requirement for sugar resorption by the tubular cells, demonstrating that the presence of a hydrogen-bond acceptor such as fluorine on C-2 is not sufficient for interaction with the receptor and subsequent resorption into the blood. The consequence of this to the whole-body distribution is important because, whereas glucose-like behavior would keep the sugar in circulation, resulting in its continued delivery to tissues, free F-18-DG in the blood is continually excreted into the urine. This factor is largely responsible for the low body background of this radiopharmaceutical and results in its prominence in organs having high hexokinase activity, such as the heart and brain, which metabolically "trap" the F-18-DG intracellularly.

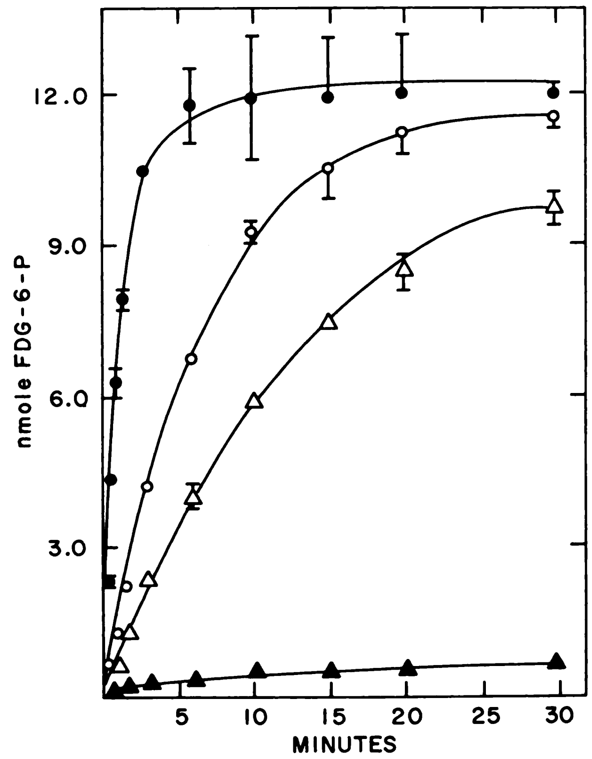


FIG. 4. Relative rates of phosphorylation of F-18-DG (12 nmole in reaction mixture) by hexokinase as measured in homogenates of brain (●—●), heart ≃ kidney (○—○), lung (△—△) and liver (▲—▲). Values are mean and range for duplicate determinations

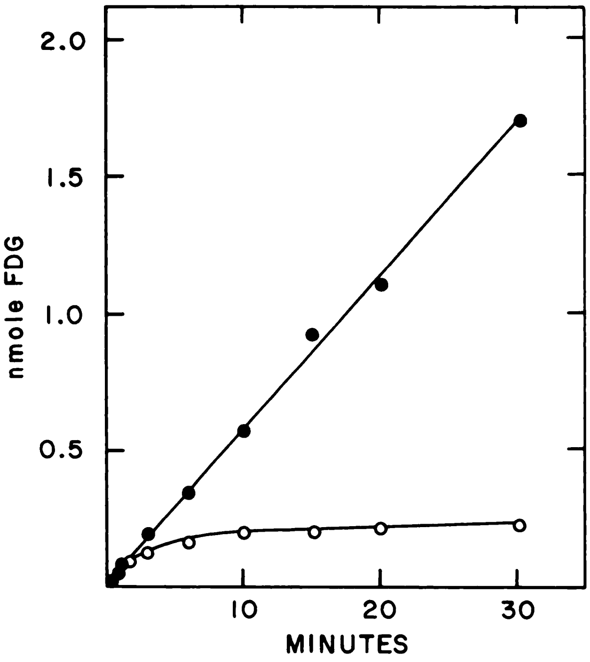


FIG. 5. Relative rates of glucose-6-phosphatase activity in liver (●—●) and kidney (○—○) using F-DG-6-P as a substrate (10 nmole in reaction mixture). Values are mean of duplicate determinations carried out in 50 millimolar cacodylate buffer at pH 6.5; the variation was less than 2%.

The extent to which the metabolism and distribution of radioactivity in brain, heart, lungs, liver, and kidneys reflects their respective hexokinase and glucose-6-phosphatase activities was investigated using organ homogenates with F-18-DG or F-18-DG-6-P in order to determine the relationship between these enzymatic values and the observed biodistribution patterns of this radiopharmaceutical.

Considering the widely different properties, functions, and metabolic demands of various mammalian tissues, it is not surprising that the hexokinase activity in many tissues is governed by complex regulatory mechanisms. Long (*19*) determined the hexokinase activity toward D-glucose in several rat tissues and demonstrated the brain > heart > kidney > lung > liver sequence in the activity per weight of tissue observed for D-glucose. The present studies in mouse tissues using F-18-DG as the substrate gave results similar to those of the earlier studies, with the exception that the kidney activity was of the same magnitude as the heart on a per-milligram-protein basis. This observation in vitro is of interest in view of the data obtained in vivo. In the intact mouse, F-18-DG phosphorylation by the heart (Fig. 1) was significantly greater than that observed for the kidney (Fig. 2), yet the biochemically measured rates of phosphorylation measured in vitro were virtually indistinguishable (Fig. 3). We believe this seeming discrepancy is most readily explained on the basis of cellular and functional compartmentalization. As discussed above, the kidney appears unable to resorb F-18-DG, based both on what is already known for the similar 2-deoxy-glucose (*17,18*) and the fact that a relatively large portion of the injected radioactivity appears in the urine as unchanged F-18-DG. The resorption of D-glucose from the renal tubules against a concentration gradient is a process that may involve phosphorylation by hexokinase. In view of this function it is not surprising that the in vitro hexokinase activity of the kidney is quite high, whereas the formation of F-18-DG-6-P from the poorly resorbed F-18-DG in vivo is relatively slow. Thus the F-18-DG filtered into the kidney tubule lumen probably never reaches the tubular cell's hexokinase.

The brain, which is totally dependent upon glucose as its energy source (*20*) rapidly phosphorylates F-18-DG both in vivo and in vitro. Virtually all of the activity present in the brain between 1 and 120 min was in the form of F-18-DG-6-P. Furthermore, the organ homogenates studied, the brain showed the highest hexokinase activity on a per-milligram-protein basis. In addition, there was no observed glucoes-6-phosphatase activity in the brain, a factor that also contributes to the retention of radioactivity.

Under normal conditions, the heart preferentially utilizes long-chain fatty acids, but under conditions of anoxia or ischemia it may rely heavily upon glucose as an energy source (*21*). The radioactivity in the heart over the time course of the study (1 min to 2 hr) was essentially all F-18-DG-6-P. In heart homogenates, hexokinase activity was less than that of brain, but apparently in the intact mouse it is sufficiently high to trap intracellularly all of the F-18-DG present in the myocardium as F-18-DG-6-P. While we are suggesting that F-18-DG uptake by myocardium may reflect glucose metabolism, it remains to be shown that this compound is transported by the same carrier-mediated system as glucose, and at a rate equal to or proportional to the glucose rate. Experiments designed to answer this question are currently in progress, using an isolated perfused heart preparation. We are also currently exploring the use of F-18-DG for myocardial metabolism studies using emission tomography.

The liver showed a rapid clearance of the initial radioactivity, a relatively slow build-up of F-18-DG-6-P in vivo and the lowest rate of phosphorylation of F-18-DG observed in vitro. The latter finding can be explained by the well-known fact that liver glycogen arises mainly through gluconeogenesis, with three-carbon fragments arising from peripheral tissues to serve as the precursors (*22*). This low rate of incorporation of glucose into glycogen by the liver (*23*) is presumably a result of the relatively low intrinsic liver hexokinase activity (*19*). Thus, the rapid clearance of radioactivity by the liver appears to reflect the back diffusion of free F-18-DG. In addition, the glucose-6-phosphatase activity that could be measured in this tissue may also contribute to the rapid clearance of F-18-DG by conversion of F-18-DG-6-P formed to free F-18-DG, which can then re-enter the blood.

Tissue slices and perfused lungs can consume relatively large quantities of glucose (*24*). Although lung function has not yet been shown to be glucose-dependent, glucose does play several important roles in the lung including entry into glycolysis (*25*). The present findings of a relatively high hexokinase activity toward F-18-DG measured in vitro, and the production of F-18-DG-6-P in vivo, are in accord with these previous findings. The 1-min values for the total radioactivity/gram are rather low, but the lung clearance of activity over the 2-hr study showed a decrease by a factor of only ~3, whereas the liver and kidney cleared by factors of ~16 and 21, respectively. Thus the relatively low initial extraction of F-18-DG accounts for the absence of appreciable F-18-DG activity in lung at later times.

CONCLUSION

In view of the present results, the biodistribution pattern of F-18-DG can be better understood. Following the i.v. administration of [^{18}F] 2-deoxy-2-fluoro-D-glucose (F-18-DG), radioactivity initially distributes to all of the organs and then rapidly clears, except from the brain and heart. This is the result of a metabolic trapping of F-18-DG-6-P by these organs, with their high hexokinase activity and low or absent glucose-6-phosphatase activity. The F-18-DG that clears from the lungs, liver, and kidney—which have lower hexokinase and/or glucose-6-phosphatase activity)—is excreted into the urine mostly as the unchanged F-18-DG. This rapid excretion substantially reduces the body-background radioactivity, contributes to the rapid blood clearance, and is the result of the apparent inability of the kidney's tubule cells to resorb F-18-DG. The net effect of these metabolic processes is that virtually all of the F-18-DG that is initially transported through the heart and brain is rapidly phosphorylated by hexokinase. Thus, the tissue content of F-18 radioactivity that can be measured in vivo by tomographic techniques might provide a measure of the ability of the brain and heart to transport, phosphorylate, and thus utilize glucose in vivo. The potential cliincal utility of F-18-DG for metabolic studies in vivo by heart and brain must rely on an understanding of the mechanisms by which F-18-DG metabolism reflects glucose utilization.

FOOTNOTES

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ERRATUM

A typographical error appears in the article entitled "Cardiac Chamber Imaging: A Comparison of Red Blood Cells Labeled with Tc-99m In Vitro and In Vivo," by F. Hegge, G. Hamilton, S. Larson, J. Ritchie, and P. Richards (*J Nucl Med* 19: 129-134, 1978). The equation appearing on p 132 should be corrected to read as follows:

$$\text{Blood-pool volume} = \text{dose volume} \times \frac{\text{cpm/cc dose}}{\text{cpm/cc blood sample}}$$