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Animal studies on the reduction and/or dilution of 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) activity in the urinary system

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To evaluate two methods for decreasing and/or diluting the FDG activity in the urinary system, five rats were intraperitoneally given 1,000 μg/g of L-lysine 4 times, starting from 60 minutes before iv injection of FDG, and then at 30-minute intervals for 90 minutes. Five rats were used as controls. In a furosemide study, 12 rats were allocated to three groups. Group 1 received iv injection of FDG alone. Group 2 received saline before iv injection of FDG. Group 3 received furosemide (7 mg/kg) and saline (1/30 of body weight). Neither renal uptake nor urinary excretion of FDG had a statistically significant difference: renal uptake; 0.179 ± 0.011 (L-lysine) vs. 0.119 ± 0.003 (control) % kg injected dose/g. The % dose excreted and total urine volume were: 15.0 ± 2.5 to 15.5 ± 2.5 with 2.98 m*l* (L-lysine), 22.9 ± 1.8 to 24.2 ± 1.5 with 1.41 m*l* (control). The furosemide study revealed a statistically significant difference: Group 1; 7.57 ± 4.73, Group 2; 0.686 ± 0.638, Group 3; 2.37 ± 2.33% kg injected dose/g ($p < 0.01$ for Group 1 vs. Group 2, $p < 0.05$ for Group 1 vs. Group 3). While pretreatment with L-lysine or furosemide failed to decrease renal activity of FDG, saline injection without furosemide markedly decreased urinary activity.

Key words: 2-deoxy-2-[^{18}F]fluoro-D-glucose, urinary system, L-lysine

INTRODUCTION

THE USE of positron emission tomography (PET) in tumor imaging and treatment response monitoring is increasing rapidly. Especially 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG), an analogue of 2-deoxyglucose, has been increasingly recognized as an excellent tumor scanning agent for the past decade because tumors commonly metabolize glucose excessively. Many animal models to endorse the potential usefulness of FDG as a tumor scanning agent have been published.[1–5] Clinical application of FDG-PET is now being established in various kinds of tumors, such as brain tumors, pulmonary cancer, breast cancer, colorectal cancer, pancreatic cancer, hepatoma, melanoma, lymphoma and the like.[6]

Genitourinary neoplasms can also be imaged by FDG-PET.[7–13] The intense FDG accumulations in the kidneys and urinary bladder hamper FDG uptake in renal and intrapelvic tumors, so that establishing methods for decreasing renal FDG uptake and urinary excretion of FDG is of clinical significance.

On the other hand, it is known that basic amino acids and their derivatives can reduce the renal uptake of ^{111}In-octreotide, -Fab fragment of a monoclonal antibody, and other radiolabeled monoclonal antibody fragments, presumably by inhibiting tubular reabsorption of glomerularly filtered peptides, although contradictory theories concerning the mechanism have been published.[14–16] The mechanism of reabsorption of FDG in the renal proximal tubule has either not been known or has not been documentated. A basic amino acid, L-lysine, might have a potential for reducing renal FDG uptake.

The aim of our study is to assess, in rodent models, three methods to potentially reduce and/or dilute FDG activity in the urinary system. We present here our results of a series of FDG studies that show whether administration of the basic amino acid L-lysine is capable of reducing renal

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uptake of FDG. We also investigated to what extent administration of saline and diuretics can reduce FDG activity in urine samples.

MATERIALS AND METHODS

L-lysine study

L-lysine (L-2,6-diaminohexanoic acid) ethyl ester dihydrochloride ($C_8H_{18}N_2O_2 \cdot 2HCl$) which was obtained from SIGMA Chemical Co. (St. Louis, MO), was dissolved in PBS (0.01 M phosphate buffer, 0.0027 M potassium chloride, 0.137 M sodium chloride; pH 7.4) to yield a concentration of 80 mg/m*l*.[16]

Ten male Sprague-Dawley rats (Charles River Breeding LABS, Wilmington, Mass) weighing 397–490 g, 3.5 months of age were used. All the rats were fasted overnight before the study. The penis of each was tied beforehand to obtain an accurate urine volume after the remaining urine was squeezed out by pressing the lower abdomen. Five rats were intraperitoneally given L-lysine solution (1,000 μg/g, approximately 5.5 m*l* per injection) 4 times, starting from 60 minutes before iv injection of FDG, and then at 30 minute intervals for 90 minutes (i.e., −60 min, −30 min, 0, 30 min). Five rats were treated with approximately 5.5 m*l* of saline as controls.

[^{18}F]fluoride was prepared with a medical cyclotron (T.C.C. model CS30). FDG was synthesized by a nucleophilic exchange fluorination method on a quaternary 4-amino-pyridium resin to produce FDG with very high specific activity (greater than 3,000 Ci/mmol).[17] Four hundred micro curies (14.8 MBq) of FDG was injected at a volume of 0.3 m*l* via the femoral vein in each rat 60 minutes after starting the L-lysine injection. All the rats were necropsied 60 minutes after iv injection of FDG. The organs were removed and blotted to minimize adhering blood. The organs and urine samples obtained were weighed, counted and their biodistributions were calculated by standard methods. ^{18}F activity was counted in a Packard automated NaI gamma counter with a 511 keV window ±20%. The activity was corrected for decay. Data were expressed as percentage kg of the injected dose per gram of tissue (% kg injected dose/g), which means % injected dose/gram normalized for a 1 kg animal. The percentage dose excreted (% injected dose/g × total urine volume) was calculated by pipetting and counting the urine obtained.

The urine samples were examined semi-quantitatively with CHEMSTRIP urine test strips obtained from Boehringer Mannheim Corporation, Indianapolis, IN.

Furosemide study

Twelve female Sprague-Dawley rats (Charles River Breeding LABS, Wilmington, Mass) weighing 200.7–240.9 g were used. All the rats were fasted overnight before the study. The rats were allocated to three groups of four. Group 1 (controls) were subjected to injection of FDG only via the tail vain (sham study). Group 2 received intraperitoneal injection of saline (1/30 of body weight per injection) 3 times, starting from 2.5 hours before FDG injection, and then at one-hour intervals for 2.0 hours (i.e., −2.5, −1.5 and −0.5 hours). In Group 3, saline was injected in the same way as in Group 2. Furosemide (Lasix) was also injected at a dose of 7 mg/kg (a volume of 0.25 m*l*) via the tail vein 30 minutes before the injection of FDG.

All the rats in Groups 1 to 3 were given 200 μCi (7.4 MBq) of FDG (0.2 m*l*). Urine samples were collected from a metabolic cage and by pressing the lower belly of each rat with the thumb three hours after iv injection of FDG. A one-hour urine volume between 3 and 4 hours after iv injection of FDG was also obtained by collecting from a urine vial and puncturing the bladder with a syringe. All the rats were necropsied four hours after iv injection of FDG. The samples were weighed. FDG biodistribution in the three groups was determined in the same way as in the L-lysine study.

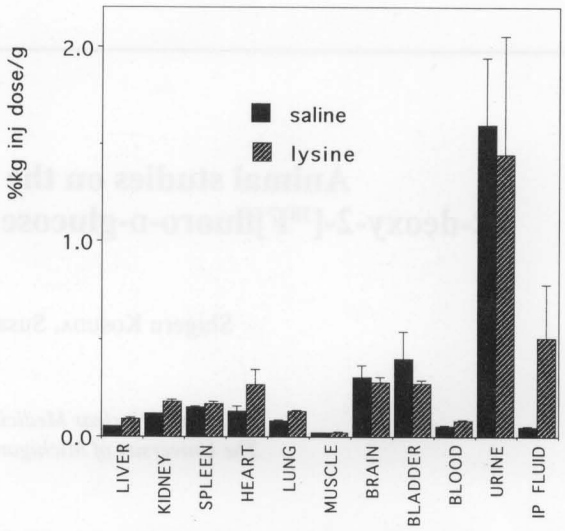

Fig. 1 FDG uptakes (% kg injected dose/g) in normal organs of the control group (n = 5) and the L-lysine pre-treated group (n = 5) at 60 min after iv injection of FDG. Note that the value of the urine is less in the L-lysine group than in the saline group, although renal values are similar in both groups. Higher values for the intraperitoneal juice and heart samples are probably due to blood contamination.

RESULTS

L-lysine study

Figure 1 shows FDG uptake (% kg injected dose/g) in rat tissues after iv injection of FDG in the L-lysine group and the control group. The values for the renal uptake of FDG were 0.179 ± 0 .011 (n = 5) % kg injected dose/g in the L-lysine group and 0.119 ± 0.003 (n = 5) % kg injected dose/g in the control group. There was not a statistically significant difference between the L-lysine and control

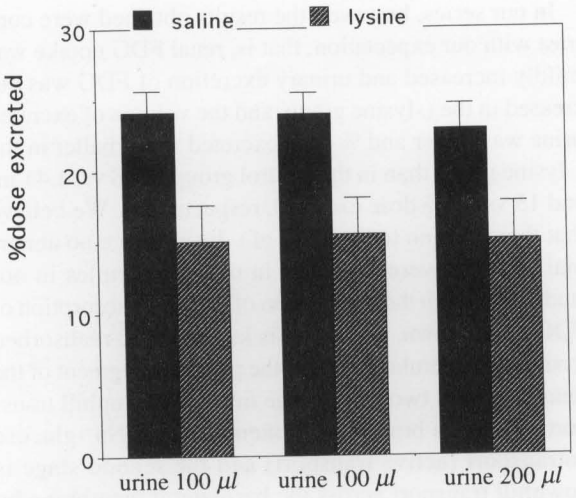

Fig. 2 Comparison of the values of % dose excreted in total urine volume between the saline and L-lysine groups.

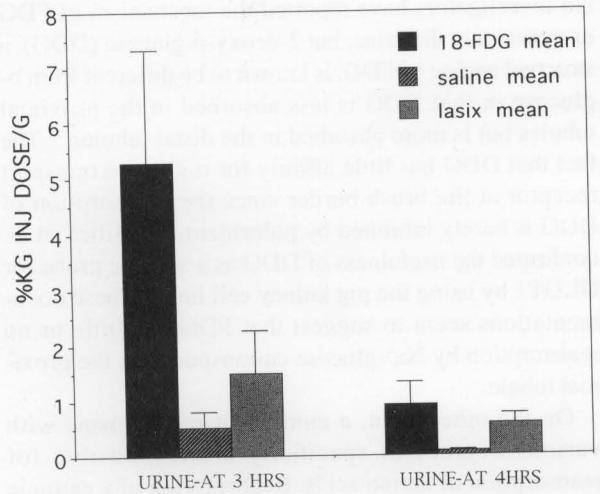

Fig. 3 Urinary excretion of FDG in three groups; control (Group 1: FDG only), saline administration (Group 2), saline plus furosemide administration (Group 3) for 3 hr and 3–4 hr after iv injection of FDG. Note that Group 2 shows the lowest activity in the urine samples.

groups in FDG uptake. Urine samples showed the highest FDG activity in the two groups, with values of 1.45 ± 0.61 ($n = 5$) and 1.60 ± 0.35 ($n = 5$) % kg injected dose/g in L-lysine and saline groups, respectively, but the values for percentage dose excreted ranged from 15.0 ± 2.5 to 15.5 ± 2.5 in the L-lysine group and 22.9 ± 1.8 to 24.2 ± 1.5 in the control group ($p < 0.01$), with total urine volumes of 2.98 vs. 1.41 m*l* on the average (Fig. 2).

In regard to urinary findings for glucose, protein, pH, leukocytes, ketones, urobilinogen, bilirubin and blood, there was no marked difference between the two groups.

Furosemide study

Figure 3 shows urinary values for % kg injected dose/g in the three groups. Pretreatment with saline alone and saline

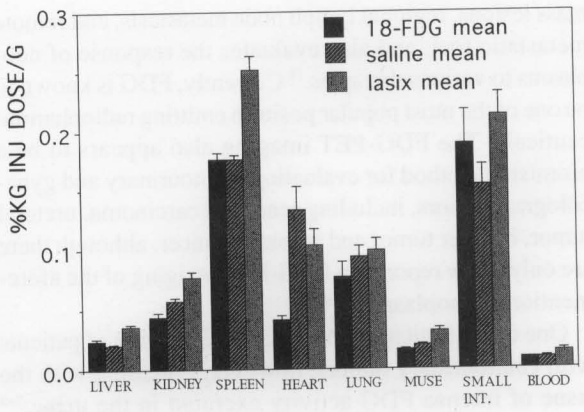

Fig. 4 FDG uptakes (% kg injected dose/gram) in normal organs of three groups; control (Group 1: FDG only), saline administration (Group 2), saline plus furosemide administration (Group 3) at 4 hr after iv injection of FDG.

plus furosemide was capable of diluting FDG activity in the urine. The urinary FDG value for the first four hours after iv injection was 7.57 ± 4.73% kg injected dose/g (0–3 h: 5.28 ± 2.05 plus 3–4 h: 1.12 ± 0.74) in Group 1, 0.686 ± 0.638 (0–3 h: 0.552 ± 0.29 plus 3–4 h: 0.232 ± 0.038) in Group 2 and 2.37 ± 2.33 (0–3 h: 1.49 ± 0.76 plus 3–4 h: 0.977 ± 0.243) in Group 3, respectively. There is a statistically significant difference in % kg injected dose/g among the three groups ($p < 0.01$ for Group 1 vs. Group 2, $p < 0.05$ for Group 1 vs. Group 3, Student-t test). The ratio of the % kg injected dose/g in Group 3 to that in Group 1 was approximately one quarter on the average. And the ratio of the % kg injected dose/g in Group 2 to that in Group 1 was approximately one tenth on the average.

The total urine weight was available from five of 12 rats, but from the remaining rats was it unavailable because of technical errors at autopsy. The total urine weights were on the average 0.132 g ($n = 2$) in Group 1 and 0.600 g ($n = 3$) in Group 3.

Figure 4 shows FDG uptakes (% kg injected dose/g) in rat tissues four hours after the intravenous injection of FDG. Renal uptake of FDG is slightly increased by administering furosemide. The % kg injected dose/g was 0.0767 ± 0.0049 in Group 3, 0.0569 ± 0.0033 in Group 2 and 0.0442 ± 0.0030 in Group 1. Pretreatment with saline alone and saline plus furosemide was unable to lower % kg injected dose/g in the blood and muscle.

DISCUSSION

L-lysine study

Increased glycolysis in neoplasms has led to the use of glucose analogues to localize neoplasms by PET. Metabolic and anatomical imaging with FDG, one of the glucose analogues, has been used successfully in miscellaneous cancers.[6–13] FDG-PET has demonstrated substantial potential in clinical oncology as a tool which depicts

mass lesions, regional lymph node metastasis, and remote metastatic foci, and also evaluates the response of neoplasms to various therapies.[18] Currently, FDG is known to be one of the most popular positron emitting radiopharmaceuticals. The FDG-PET imaging also appears to be a promising method for evaluating genitourinary and gynecological tumors, including renal cell carcinoma, ureteral tumor, bladder tumor and prostatic cancer, although there are only a few reports on FDG-PET imaging of the aforementioned neoplasms.[7-9,13]

One of the limitations of FDG-PET imaging of patients with genitourinary tumors, however, is dealing with the issue of intense FDG activity excreted in the urine.[7-9] Urinary excretion of FDG has been reported to be 16% and 50% of the injected dose at 60 and 135 minutes after the injection in canine studies.[19] Intense FDG activity in the urinary bladder degrades the image quality in FDG-PET, resulting in blurs in depicting the anatomic localization and tumor uptake of FDG in the pelvic cavity. Obstruction or stenosis of the urinary collecting system hampers accurate interpretation of the renal images, resulting in decreased sensitivity of FDG-PET in detecting small tumors and lymph node involvement located in the retroperitoneal region. There are also reports indicating that FDG is substantially taken up by the renal parenchyma.[9,20] And another report said that the value for renal uptake of FDG was $1.14 \pm 0.11\%$ inj dose/g in mice and 0.62–0.97% inj/organ in dogs.[19] These findings suggest poor interpretation of renal images obtained by FDG-PET for renal cell carcinoma. Decreasing renal uptake and urinary excretion of FDG is therefore a clinical challenge for the accurate interpretation of FDG images of intrapelvic and/or retroperitoneal neoplasmas.

Basic amino acids, such as L-lysine and L-arginine, are known to be able to induce functional proteinuria and reduce renal reabsorption of protein when given in high doses. Three previous studies showed that amino acids including L-lysine were effective in lowering the renal uptake of radiolabeled octreotide and Fab′ fragments.[14-16] Morgenson and Sølling reported that infusion of lysine and arginine blocked renal tubular peptide reabsorption.[21] While precise information on FDG reabsorption in the renal tubules has not yet been obtained, FDG might have a tubular reabsorption mechanism in common with L-lysine because both deoxyglucose and basic amino acid are incorporated into the cell by facilitated diffusion.[22] High dose administration of positive charged L-lysine might also inhibit tubular reabsorption of FDG by competitive reaction to a transporter. There is another theory that simple neutralization of negative charges of the luminal tubular cell surface by positively charged molecules hinders the reabsorption of glomerularly filtered substances.[16] These theories lead us to infer that pretreatment with L-lysine would result in a decrease in the renal uptake of FDG and an increase in the urinary excretion of FDG.

In our series, however, the results obtained were contrast with our expectation; that is, renal FDG uptake was mildly increased and urinary excretion of FDG was decreased in the L-lysine group, and the volume of excreted urine was larger and % dose excreted was smaller in the L-lysine group than in the control group (2.98 vs. 1.41 m*l* and 15 vs. 23% dose excreted, respectively). We believe that there was no toxic effect of L-lysine since no abnormal findings were observed in urinary samples in our study. Although the mechanism of tubular reabsorption of FDG is unknown, D-glucose is known to be reabsorbed from the glomerular filtrate in the proximal segment of the renal tubule in two stages. The first stage is uphill transport across the brush border membrane by Na^+-glucose cotransport (active transport) and the second stage is downhill transport across the basolateral membrane by facilitated diffusion (passive transport; GLUT1 or 2).[23-27]

The most conspicuous difference between D-glucose and FDG is probably that FDG is excreted into the urine. No investigators have reported the mechanism of FDG excretion into the urine, but 2-deoxy-D-glucose (DDG), a structual analog of FDG, is known to be different from D-glucose in that DDG is less absorbed in the proximal tubules but is more absorbed in the distal tubules.[28] The fact that DDG has little affinity for D-glucose transport receptor at the brush border since the reabsorption of DDG is barely inhibited by phloridzin.[29,30] Miller, et al. confirmed the usefulness of DDG as a specific probe for GLUT1 by using the pig kidney cell line.[31] These documentations seem to suggest that FDG has little or no reabsorption by Na^+-glucose cotransporter in the proximal tubule.

On the other hand, a number of mechanisms with various degrees of specificity are responsible for reabsorption of amino acids. Reabsorption of a cationic amino acid, L-lysine, mainly relies on a sodium-independent transport system, i.e., a process called facilitated diffusion, system y^+, while neutral amino acids are reabsorbed by sodium-cotransport.[22,32]

If FDG is reabsorbed mainly by GLUT1 in the renal tubules, pre-treatment with high-dose DDG might interact with tubular reabsorption of FDG, although high-dose DDG inhibits hexokinase activity and would be highly toxic, even in animal preparations. Additional study will be necessary to assess the mechanism of FDG reabsorption and the decrease in renal uptake of FDG.

Furosemide study

In Group 2 pretreated with saline alone, % kg injected dose/g for urinary excretion of FDG was significantly decreased (Fig. 3). The ratio of the % kg injected dose/g in Group 2 to that in Group 1 was approximately one tenth on the average. But the pretreatment with saline plus furosemide resulted in higher values for % kg injected dose/g than those following pretreatment with saline alone, and mildly increased renal uptake of FDG. It is well

documented that thiazide diuretics bring about exacerbation of glycemic control in diabetic patients.[33,34] Furosemide also causes acute hyperglycemia and reduces glucose tolerance.[35,36] Fuhrman FA published a report stating that severe potassium depletion in animals caused abnormal carbohydrate tolerance.[37] Although we are unable to elucidate the mechanism by which the % kg injected dose/g became higher when furosemide was iv injected, we speculate that it is attributable to decreased tolerance of FDG and to hypokalemia induced by furosemide. In this study, we employed furosemide at a dose of 7 mg/kg as a diuretic, but a smaller amount of furosemide or other diuretics appears likely to further decrease the % kg injected dose/g for urinary excretion of FDG.

According to the observation at four hours after iv injection of FDG, administration of saline alone or saline plus furosemide was unable to lower the % kg injected dose/g of the blood and muscle. Furosemide, on the contrary, increased the % kg injected dose/g in all tissues except the heart, suggesting that administration of furosemide 30 minutes prior to FDG injection results in dehydration. Dehydration might lead to degradation of image quality with a higher lesion-to-background ratio in the clinical setting. Patients have generally been forbidden to take any food for at least 4 hours before an FDG-PET study. Taking some water is, however, required, thereby making it possible to decrease exposure to FDG in the urinary system and helping us interpret the FDG-PET image with a greater confidence. Nevertheless, further studies will be needed to determine the optimal time for the injection of furosemide.

An excessive load of water without diuretics would therefore actually be actually useful in lowering the specific activity of the FDG excretion in the clinical setting. Although it remains to be determined whether drip infusion of saline is an optimal form of fluid supplement, it will be helpful for assessing FDG-PET images in patients with intrapelvic tumor, especially those with bladder tumor and ureter tumor. Because the rapid urinary excretion of FDG hampers the accurate interpretation of PET images, it is necessary to perform retrograde irrigation of the bladder with a Foley catheter. Harney, et al. found in rats with bladder cancer that tumor-to-normal bladder ratios were less than 0.5 with the absence of lavage, but 9.1 after irrigation with 1 m*l* saline, and 13.1 after 5 m*l* saline irrigation,[7] suggesting that the longer the irrigation time and the higher the volume of saline are, the higher the tumor-to-normal bladder ratio is. The delayed imaging of PET is inappropriate because the physical half-life of ^{18}F is 110 minutes, although urinary activity of FDG may be decreased and tumor activity of FDG may be increased with time. This must await further studies with a tumor model.

In conclusion, the pretreatment with L-lysine or furosemide failed to lower the renal activity of FDG in our animal study, but an administration of saline without furosemide before injection of FDG seems to significantly decrease urinary activity. This may have important implications for improving the pelvic image quality in FDG-PET imaging in patients with genitourinary neoplasms.

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