(F-18)-2-Deoxy-2-Fluoro-D-Galactose: A Potential Tracer for the Assessment of Sugar Metabolism in the Liver by Positron Emission Tomography

III. 19 (F-18)-2-Deoxy-2-Fluoro-D-Galactose: A Potential Tracer for the Assessment of Sugar Metabolism in the Liver by Positron Emission Tomography

Fukuda H., Matsuzawa T., Tada M.*, Ohrui H.**, Takahashi T.***, Yamada K., Yoshioka S., Ito M., Abe Y., Sato T., and Ido T.***
Department of Radiology and Nuclear Medicine, The Research Institute for Tuberculosis and Cancer, Tohoku University
Department of Pharmacology, The Research Institute for Tuberculosis and Cancer, Tohoku University*
Department of Food Chemistry, Faculty of Agriculture, Tohoku University**
Cyclotron and Radioisotope Center, Tohoku University***

Introduction

There were few positron labeled tracers available for liver imaging. Although Ga-68-labeled microsphere (1) is available, this agent was indicator of reticuloendothelial system and do not directory reflect hepatocellular biochemical function. Gallium-68 BP-IDA (2) is also available and it reflects the uptake and secretary function of hepatocells. However, quantitative measurement of hepatocellular metabolism is not difficult because it is not trapped by the liver.

In this study, we newly synthesized (F-18)-2-deoxy-2-fluoro D-galactose and examined its potential for the assessment of regional liver function by positron emission tomography. In this preliminary evaluation, biodistribution studies were made in normal rats. An autoradiogram of rat and rabbit, and imaging of rabbit liver by positron emission tomography were also performed.

Materials and Methods

Synthesis of (F-18)-2-deoxy-2-fluoro-D-galactose ((F-18)-FDGal)

The agent was synthesized by the analogous method as (F-18)-2-deoxy-2-fluoro-D-glucose ((F-18)-FDG). Details of synthesis procedure was described elesewhere (in preparation). The radiochemical purity of the radiopharmaceutical determined by HLPC was 98-99% and specific activity was 10-15 mCi/mg.

Biodistribution study

Male Donryu rat (weighing 120-140g) was used for tissue distribution study. (F-18)-FDGal in isotonic saline was injected IV into rats through the lateral tail vein. The rats were killed by neck dislocation at 10, 30, 60, 120 and 180 min after injection. The blood and organs were removed, blotted, weighed and counted in an automated NaI well-counter and the radioactivities corrected for decay. Data were expressed as percent injected dose per gram of tissue.

Positron emission tomography

Just after the IV injection of 2 mCi of F-18-FDGal into a cotton-tail rabbit, the sequential liver scans for every 3 min was started. The total data aquisition time was about 60 min. Each scan had a total count of 1000-2000 K

counts. The liver image was obtained by positron emission tomography (ECAT-II, ORTEC) with a medium resolution shadow shields, medium resolution data aquisition mode and medium resolution filter function. The resolution of this mode was 13-14 mm (FWHM).

Autoradiography

Autoradiograms of rat, which received with 2 mCi of F-18-FDGal, were made 30 min after injection. The rats were killed by chloroform, frozen by dry ice + aceton and sliced 30-40 μm thick with an autocryotome. The slices were contacted to ^{3}H-type Ultrafilm (Sakura, Co Ltd) and the films were exposed for 12 hours in the dark room and then developed.

Results

Biodistribution study

Figure 1 showed the tissue distribution of (F-18)-FDGal in the rats as expressed percent injected dose per gram of tissue. The values were normalized to per 100 g body weight because of neglecting the differences of body weight. The liver uptake was rapid and high, giving 5.3% at 10 min, reached a peak (10.0 % dose/g) at 30 min and remained relatively constant up to 180 min. The blood clearance was very rapid and the level was nearly constant and negligible after 60 min. The kidney uptake was relatively high but about one-fourth of that of liver. The brain and soft tissue uptake was very low.

Autoradiogram

Figure 2 showed an autoradiogram of whole rat received with (F-18)-FDGal. Extremely high activities were seen in the liver but not in the bilialy system. The uptake of the kidney was the second to the liver. The uptake of other tissue was very low. These were consistent with the results of tissue distribution study.

Positron emission tomography

Figure 3 showed the time activity curve of the region of interest in the liver obtained by sequential 3-min scan. The liver count increased rapidly after injection, reached a peak at 15-20 min and maintained same level of activity over the one-hour study period. The blood clearance curve obtained from blood sampling was superimposed on the graph, showing a very rapid clearance.

Figure 4 showed the positron tomogram of the rabbit liver obtained 30 min after F-18-FDGal injection. The liver was clearly delineated with a sharp margin and high contrast.

Discussion

2-deoxy-D-galactose, which is one of the galactose analogs, is transported by the same carrier that transports galactose, and well phosphorylated to 2-deoxy-D- galactose-1-phosphate by galactokinase. However, 2-deoxy-D- galactose-1-phosphate do not enter the further step of Leloir pathway, because of very low

affinity of UDP-flucose:galactose- 1-phosphate uridyltransferase for 2-deoxy-D-galactose-1-phosphat (Fig. 5). There is no galactose-1-phosphatase activity in the liver, therefore, 2-deoxy-D-galactose-1-phosphate once formed, remains trapped in the liver (3-8).

It is suggested from the biodistribution study that (F-18)-FDGal may act like as 2-deoxy-D- galactose and that (F-18) FDGal was phosphorylated in the similar way to 2-deoxy-D-galactose, which might be analogous relation between (F-18) FDG and 2-deoxy-D-glucose.

Our preliminary results suggest that (F-18)-FDGal is trapped in the liver as a result of the phosphorylation process, and therefore might be used for studies of sugar metabolism of healthy and diseased liver, as is done with F-18-2-deoxy-2-fluoro-D-glucose in the brain.

References

1) Ishioka K., Kuniyasu Y., Higashi S., Kakei H., Hayes R. L. and Carlton J. E., Proceeding of the Third World Congress of Nuclear Medicine and Biology 662-665, 1982 Paris.
2) Shuhmacher J. S., Clorius J. H. and Czygan P., Proceedings of the Third World Congress of Nuclear Medicine and Biology 658-661, 1982 Paris.
3) Kleinzeller A. and McAvoy E. M., Biochimica et Biophysica Acta 455 (1976) 126.
4) Henderson P. J. F. and Giddens R. A., Biochem. J. 168 (1977) 15.
5) Jaspers H. T. A. and Steveninck J. V., Biochimic et Biophysica Acta 469 (1977) 292.
6) Smith D. F. and Keppler D. O. R., Eur. J. Biochem. 73 (1977) 83.
7) Starling L. J. and Keppler D. O. R., Eur. J. Biochem. 80 (1977) 373.
8) Starling L. J. and Keppler D. O. R., J. Neurochem. 29 (1977) 603.

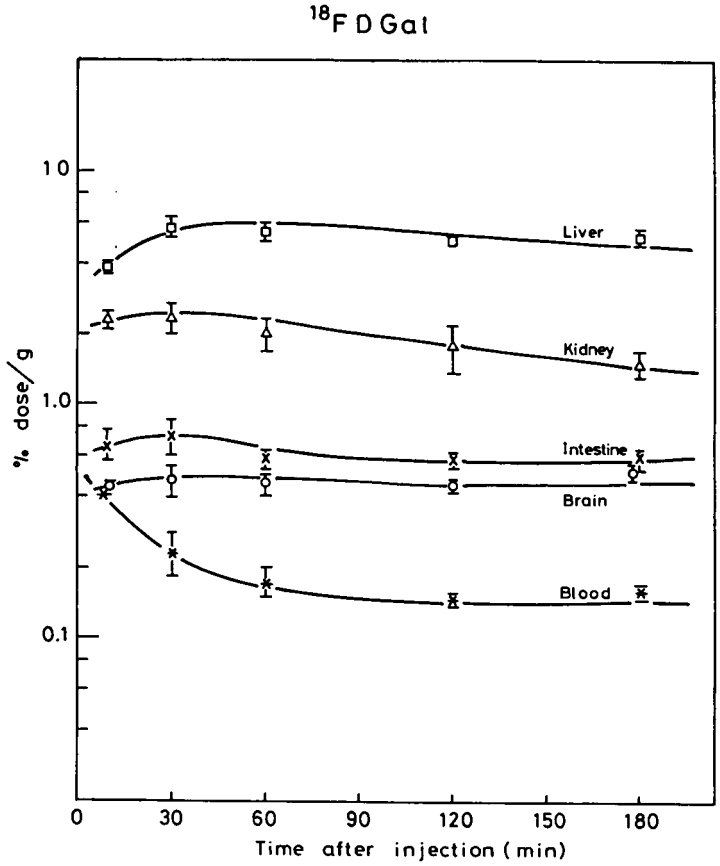

Fig. 1. Tissue distribution of ^{18}F-FDGal in Donryu rat.

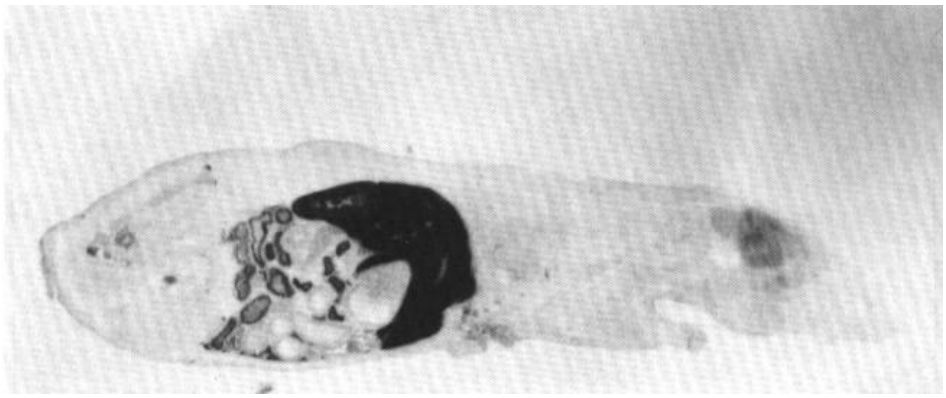

Fig. 2. Autoradiogram of whole rat received with ^{18}F-FDGal (30 min after injection).

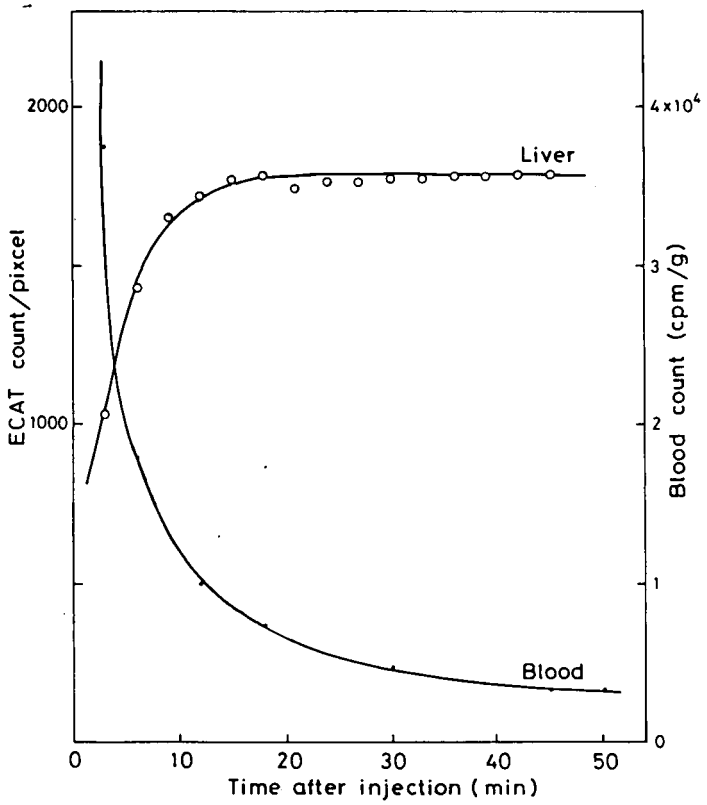

Fig. 3. Time-activity curve of ROI in the rabbit liver (o—o). Blood clearance curve obtained by blood sampling was superimposed on the graph (•—•).

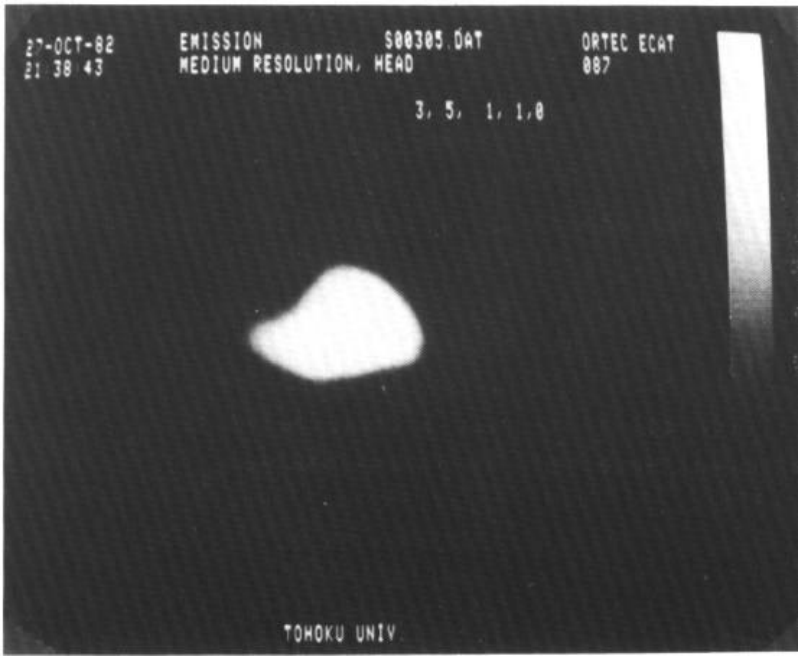

Fig. 4. Positron emission tomograph of rabbit liver.

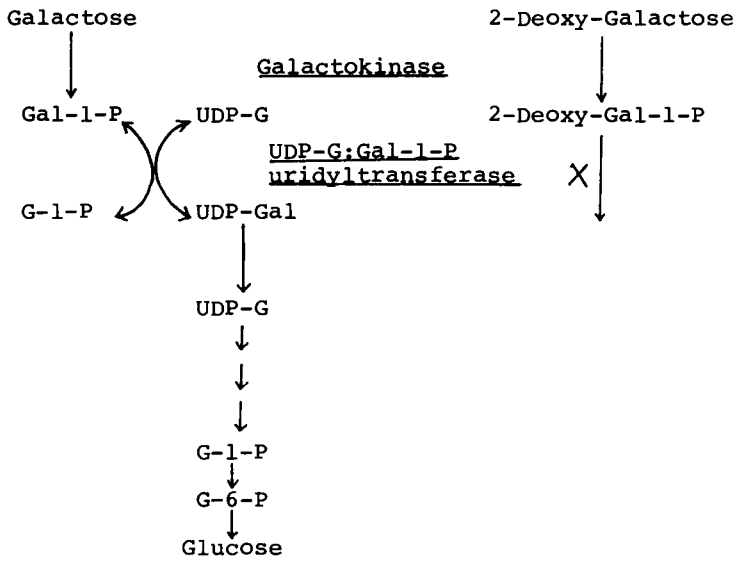

Fig. 5. Metabolic pathway of galactose and 2-deoxy-galactose.