Communications to the Editor

[Chem. Pharm. Bull.]
[35(2) 895-897 (1987)]

NMR EVIDENCE FOR THE UNEXPECTED INTERCONVERSION OF
2-DEOXY-2-FLUORO-D-GLUCOSE AND 2-DEOXY-2-FLUORO-D-MANNOSE IN MICE

Yoko Kanazawa,^a Yuko Momozono,^a Hideki Yamane,^b
Terushi Haradahira,^a Minoru Maeda,^a and Masaharu Kojima^a

Faculty of Pharmaceutical Sciences,^a and Faculty of Medicine^b,
Kyushu University 62, Higashi-ku, Fukuoka 812, Japan

2-Deoxy-2-fluoro-D-glucose (FDG) or its 6-phosphate (FDG-6-P) was detected by ¹⁹F NMR in the organs and urine of mice previously injected with 2-deoxy-2-fluoro-D-mannose (FDM). This conversion of FDG(-6-P) to FDM(-6-P) in vivo was reversible.

KEYWORDS — 2-deoxy-2-fluoro-D-glucose; 2-deoxy-2-fluoro-D-mannose; epimerization; in vivo NMR; ¹⁹F NMR

Regional glucose utilization has been determined in man with the aid of 2-deoxy-2-[F-18]-fluoro-D-glucose (¹⁸FDG) and positron emission tomography (1). This procedure is based on the principle that FDG is trapped in tissues of high glucose-metabolism activity in the form of FDG-6-phosphate (FDG-6-P) and that further metabolism is inhibited by the absence of an OH group at the C(2) position. However, we have shown by ¹⁹F NMR the formation of α- and β-FDM and/or FDM-6-P in significant amounts in tissues of FDG-injected mice (2). This may require modification of the compartment model used in the rate analysis of glucose metabolism in vivo. Moreover, in the present study we have demonstrated the reverse conversion, from FDM(or FDM-6-P) to FDG(or FDG-6-P). Thus, in mice these fluorinated hexoses undergo significant interconversion.

FDG and FDM were prepared by the method reported previously (3) and FDG-6-phosphate (FDG-6-P) was prepared according to a reported procedure (4). Male mice (6-7 week-old, ddY strain) were used after 16 hours of fasting. Following the intravenous injection of fluorinated hexoses (0.2 g/kg), the animals were sacrificed at various time intervals, the organs were removed, washed immediately, and kept frozen pending NMR measurements. ¹⁹F NMR spectra of organs and of urine were taken with a JEOL FX-100 standard high resolution spectrometer operated at 93.7 MHz at ambient temperature (25 ± 1°C) in a 10-mm OD sample tube at the spectral width of 50 kHz. Hexafluorobenzene (HFB) was used as an external standard to measure chemical shifts.

α-, β-FDG, α-, β-FDM, α-, and β-FDG-6-P dissolved in water gave spectra centered at -32.3, -32.2, -37.6, -56.0, -32.4, and -32.2 ppm, respectively. The separation between FDG and α- or β-FDM was sufficient for their identification

in vivo, whereas the positions for the signals of α -, β -FDG, α -, and β -FDG-6-P severely overlapped. Extra small signals were observed in the sample of FDG-6-P in the vicinity of α - and β -FDM were attributed to the 6-phosphate of FDM(FDM-6-P) produced by the phosphorylation of FDM present in the FDG starting material (ca. 4%). Again, those 6-phosphates were not distinguishable from FDM in tissue.

Fig. 1. ^{19}F NMR Spectra (93.7 MHz) of the Organs of FDM Injected Mice. The Chemical Shifts were Measured from External HFB. A, FDG(-6-P); B, α -FDM(-6-P); C, β -FDM(-6-P).

The ^{19}F spectra of organs and urine excised or collected at various time after FDG or FDM injection are shown in Figs. 1 - 3. The spectra of specific organs of FDM-injected mice showed clearly the presence of FDG (Fig. 1). The concentration of FDG relative to FDM increased with time prior to the excretion of entire fluorinated compounds from these organs. This was similar to the earlier finding that FDG-injected mice formed FDM (Fig. 2)(2). The spectra for the urine samples

Fig. 2. ^{19}F NMR Spectra of the Organs of FDG Injected Mice. The Notation of the Signals are as in Fig. 1.

Fig. 3. ^{19}F NMR Spectra of Urine Excreted from FDG- or FDM-Injected Mice
(a) Urine of FDG-Injected Mice. (b) Urine of FDM-Injected Mice.

are shown in Fig. 3. The excretion of the main metabolites α - and β -FDM in the case of FDG injection and of FDG in the case of FDM injection is clearly evident. The other metabolite at -31 ppm is presumably the oxidation product of FDG, 2-deoxy-2-fluoro- δ -phosphogluconolactone and/or 2-deoxy-2-fluoro-6-phosphogluconate, as suggested by Nakada et al.(5). The origin of the other signals were not identified, but may include oxidation products of FDM.

A preliminary experiment showed that FDG-6-P was converted to FDM-6-P in the buffer solution containing phosphoglucose isomerase while no change was observed in the FDG-6-P solution without the enzyme. This indicates the site of interconversion.

ACKNOWLEDGEMENT This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education(No. 59460194 and 61570512).

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(Received November 28, 1986)