INVITED COMMENTARY

FDG Metabolism: *Quaecumque Sunt Vera . . .*

Our understanding of the metabolism of ^{18}F-FDG is no exception to the axiom that erosion and refinement of scientific dogma occur continuously through discovery. Although the theory and kinetic modeling for FDG were originally based on analogy to 2-deoxy-D-glucose, improved methods of chemical analysis have shown that FDG metabolism is considerably more complex. Discoveries of FDG metabolism beyond initial phosphorylation are contributors to the evolving understanding of FDG in diagnostic (nuclear) medicine. For example, although 2-deoxy-2-fluoro-D-mannose (FDM) metabolites have not yet been reported in humans, metabolic epimerization has been established in several species, and reports that FDM metabolites may account for the majority of radioactivity present in tissues at intermediate time intervals suggest that model reevaluation may be appropriate. Current kinetic models for quantification of glucose utilization by the FDG method do not account for such additional metabolic compartments. However, it appears as though the contemporary models are still acceptable under certain conditions.

Fluorine contributes unique properties to organic molecules: Its size lies between that of hydrogen and hydroxyl, its polarity is similar to that of hydroxyl, and it has the ability to hydrogen bond as a hydrogen acceptor but not as a hydrogen donor. Fluorinated compounds are attractive for biochemical studies because their biochemical properties mimic those of their nonfluorinated analogs in some respects but not in others. For example, they may enter biochemical pathways, with untoward results (e.g., specific enzyme inhibition). Furthermore, there is little or no fluorine background to complicate analysis (e.g., for ^{19}F nuclear magnetic resonance [NMR]) in biologic tissues. 6-Deoxy-6-fluoro-D-glucose was the first fluorocarbohydrate synthesized (*1*) in the search for fluorocarbohydrates. ^{19}F-FDG followed more than a quarter century later because of the challenging fluorine chemistry. The goal was achieved by nucleophilic cleavage of the epoxide to fluorinate 1:6,2:3-dianhydro-4-*O*-benzyl-β-D-altropyranose with KHF_2 (*2*) and, shortly thereafter, by electrophilic addition of CF_3OF to the triacetylglucal precursor (*3*). The latter synthesis produces the C-2 epimer, FDM, in almost equal yield, which creates a problem for radiochemists using ^{18}F. This seemingly trivial problem was perceived to be important to the FDG model, and limited ^{18}F-FDM content remains as a criterion of purity for FDG.

The demonstrated applicability of FDG for the measurement of regional glucose utilization for medical diagnoses (*4*) prompted improvements in fluorination chemistries. Today nucleophilic displacement reactions are used in the synthesis of FDG from protected mannose analogs that have appropriate leaving groups, using commercially available black boxes, although electrophilic addition of ^{18}F (*5*) is still used in some settings.

^{19}F-FDG has lived up to early expectations as a biochemically active antimetabolite of glucose. It inhibits glycolysis in ascites tumor cells (*6*), interferes with carbohydrate metabolism in some species (inhibits cell wall formation in yeast) (*7*), and is toxic to selected tumor cell lines (*8*). The transient toxicity of FDG has been attributed to both radiation effects and the biochemical effects of unidentified transient chemical species arising on decay of the ^{18}F substituent. The latter toxicities were seen at concentrations several orders of magnitude greater than those encountered during in vivo clinical studies with FDG (*9*). However, electroencephalographic abnormalities (*10*) and behavioral changes (*11*) have been reported at ^{19}F-FDG doses of $>$200 mg/kg in rats, which are near the concentrations required for MRI studies. FDG has been shown to be a substrate for hexokinase (*12*) and to be transported by the glucose transporter GLUT-1 (*13*,*14*).

The current success of PET can be largely attributed to the widespread acceptance of FDG as a diagnostic agent in neurology, cardiology, and oncology. Sokoloff et al. (*15*) developed the biochemical and kinetic models for the autoradiographic determination of regional glucose metabolism using ^{14}C-2-deoxyglucose (DG) in the rat, and others subsequently showed that the DG model could be applied to the determination of glucose utilization in human brain (*16*), heart (*17*), and tumor (*18*), using FDG and PET. The kinetic model is based on (a) a biochemical model of reversible, transport-facilitated diffusion of FDG into the cell (K_1/k_2) and (b) largely irreversible hexokinase-mediated phosphorylation (k_3/k_4; $k_3 \gg k_4$) of FDG to ^{18}F-FDG-6-phosphate (FDG-6-P), the terminal metabolite. Although the question of transport may have been complicated by the discovery of additional glucose transporters in the ensuing years (*19*), the original models have generally enjoyed broad acceptance, with irreversible phosphorylation rather than transport as the rate-limiting event. Perhaps the most critical challenges to this model to date have been the possible reverse

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conversion of FDG-6-P to FDG by glucose-6-phosphatase, which would allow FDG to escape from the cell (increased k_2) and thus lead to underestimation of FDG phosphorylation (*20*). Additionally, the ratios of transport activity to hexokinase activity may combine so that phosphorylation (k_3) is not the rate-limiting step in FDG-6-P accumulation (*21*).

The first study of FDG metabolism beyond FDG-6-P reported insignificant conversion of FDG-6-P to the corresponding FDG-phosphogluconate (FDG-6-PG1) and tentatively identified FDG-nucleotide metabolites in Rous sarcoma tumors in vivo in rats (*20*). The potential to use ^{19}F-FDG MRI to model for glucose metabolism in vivo motivated a series of ^{19}F-FDG NMR studies beginning in the mid-1980s. ^{19}F NMR analysis of metabolites in mice showed not only the presence of ^{19}F-FDG and ^{19}F-FDG-6-P but also, unexpectedly, FDM and its 6-phosphate (FDM-6-P), the latter being more prevalent in some tissues than ^{19}F-FDG-6-P (*22,23*). Indirect evidence for conversion of ^{19}F-FDG-6-P to FDM-6-P by phosphoglucose isomerase has been presented (*24*). This FDG–FDM interconversion (through their 6-phosphates) has been shown to reach a 1:4 concentration in favor of FDM at equilibrium (*25*).

The reported formation of ^{19}F-FDG-6-PG1 and 2-deoxy-2-fluoro-phosphogluconolactone in rat brain (*26,27*) could not be confirmed in mouse brain studies (*11*). However, as with ^{19}F-FDG in rat, FDG-6-PG1 has now been reported to be a major accumulated metabolite in pig liver after injection of FDG (*28*). The first and only report of the formation of an ^{19}F-FDG catabolite, 2-fluoro-2-deoxyglycerol, was reported by Nakada et al. (*10*) in an ^{19}F NMR study at 4.7 T.

Another ^{19}F NMR study has confirmed that ^{19}F-FDG and FDM are substrates for hexokinase, phosphoglucose isomerase, phosphoglucomutase, and uridine diphosphate–glucose pyrophosphorylase. Six metabolites (the -1-P, -1,6-di-P, and nucleoside diphosphate derivatives of both ^{19}F-FDG and FDM), in addition to FDG-6-P, FDM, and FDM-6-P, were found in murine brain after doses of ^{19}F-FDG (*11,29*). These authors concluded that despite this extensive metabolism, the original FDG kinetic model was satisfactory as long as analyses were performed within the first 30 min after injection, but, after 60 min, epimerization and elaboration of metabolites beyond FDG-6-P gain sufficient importance as to create additional kinetic compartments. The FDG-nucleotide metabolites (*20*) have also been confirmed and further characterized by ^{19}F NMR. NMR evidence for the importance of uridine diphosphate–FDM in the retained metabolite pool has challenged the dogma of the role of glucose-6-phosphatase in the variable (tissue to tissue) retention of FDG metabolites (e.g., FDG-6-P), especially at longer intervals after dosing (*29*). This study (*28*) of FDG metabolism in porcine liver essentially echoes the conclusions of earlier ^{18}F and ^{19}F studies: The existing kinetic models are adequate for early studies, whereas the increasingly complex metabolic profile necessitates the inclusion of additional kinetic parameters for an accurate interpretation of FDG-derived radioactivity within a specific tissue.

Several detailed FDG reviews (*30,31*) and a recent summary of FDG in PET (*32*) have been published. Unfortunately, although these reviews (*30,31*) present excellent overviews of glucose metabolism in general, they do not provide a comprehensive picture of FDG metabolism as it stands today. Clearly, the simple biochemical model of FDG to FDG-6-P may be adequate for medical imaging and estimation of glucose consumption in many clinical circumstances, but post-FDG-6-P metabolism is a reality that cannot be ignored.

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