^{18}F-FDG Radiosynthesis: A Landmark in the History of PET

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Virtually all of the brain's energy derives from glucose metabolism. This underpins the development of ^{18}F-FDG, a radiotracer that was first used to measure regional brain glucose utilization in humans, and has had a profound influence on research in the neurosciences (*1*). The subsequent discovery that ^{18}F-FDG can be used to assess viable myocardium and also accumulates in tumors in proportion to their degree of malignancy underpins the evolution of PET as a major clinical tool in cancer diagnosis and monitoring of treatment.

The 1986 landmark paper by Hamacher and colleagues in *JNM* represents a major milestone in the present use of ^{18}F-FDG in clinical nuclear medicine worldwide (*2*).

The ^{18}F-FDG molecule was modeled on the ^{14}C-labeled 2-deoxyglucose method, which measures regional brain glucose utilization in animals (*3*). 2-deoxyglucose is an analog of glucose in which the hydroxyl group on C-2 is replaced by a hydrogen atom. It mimics glucose in serving as a substrate for hexokinase, the rate-limiting step in glycolysis, but does not undergo further steps in the conversion of glucose to energy. Its translation to humans required the development of a radiolabeled version of the 2-deoxy-D-glucose molecule that maintained its biochemical properties and could be labeled with a radioisotope suitable for external imaging in humans. A survey of the literature at the time revealed that 2-deoxy-2-fluoro-D-glucose (in which the hydrogen atom on C-2 was replaced by a fluorine atom) met these requirements. An electrophilic reaction with ^{18}F using elemental fluorine ($[^{18}F]F_2$) produced via the ^{20}Ne(d,α)^{18}F reaction on Brookhaven's 152-cm (60-in) cyclotron (*4*) was developed and used to produce ^{18}F-FDG in sufficient yield for transport from Long Island to the University of Pennsylvania for the first human studies in 1976 (*1,5*).

Over the next 10 years, the demand for ^{18}F-FDG grew. This created the need for a simpler and higher-yield radiosynthesis that would be more amenable to automation and regional distribution. Indeed, the electrophilic radiosynthesis had shortcomings.

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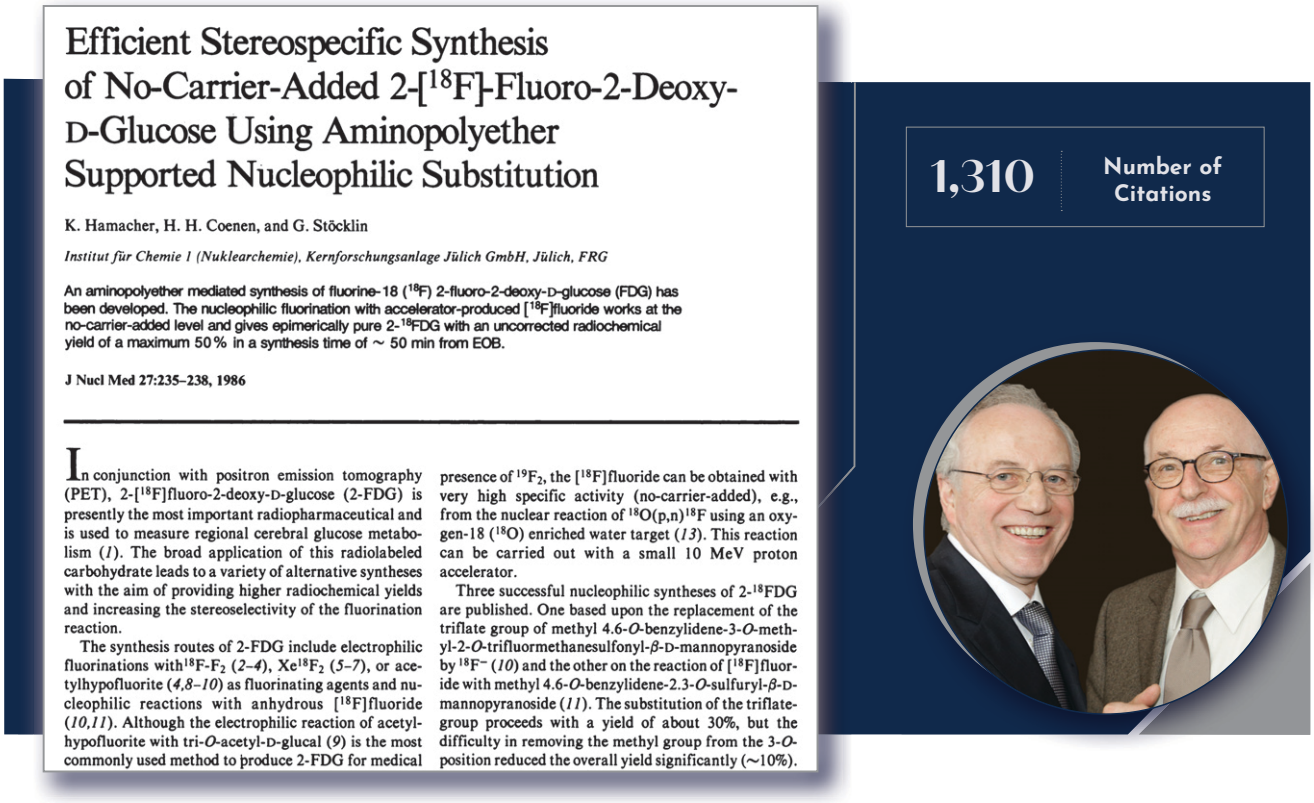

Efficient Stereospecific Synthesis of No-Carrier-Added 2-[^{18}F]-Fluoro-2-Deoxy-D-Glucose Using Aminopolyether Supported Nucleophilic Substitution

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An aminopolyether mediated synthesis of fluorine-18 (^{18}F) 2-fluoro-2-deoxy-D-glucose (FDG) has been developed. The nucleophilic fluorination with accelerator-produced [^{18}F]fluoride works at the no-carrier-added level and gives epimerically pure 2-^{18}FDG with an uncorrected radiochemical yield of a maximum 50% in a synthesis time of ~ 50 min from EOB.

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In conjunction with positron emission tomography (PET), 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-FDG) is presently the most important radiopharmaceutical and is used to measure regional cerebral glucose metabolism (*1*). The broad application of this radiolabeled carbohydrate leads to a variety of alternative syntheses with the aim of providing higher radiochemical yields and increasing the stereoselectivity of the fluorination reaction.

The synthesis routes of 2-FDG include electrophilic fluorinations with ^{18}F-F_2 (*2–4*), Xe$^{18}F_2$ (*5–7*), or acetylhypofluorite (*4,8–10*) as fluorinating agents and nucleophilic reactions with anhydrous [^{18}F]fluoride (*10,11*). Although the electrophilic reaction of acetylhypofluorite with tri-*O*-acetyl-D-glucal (*9*) is the most commonly used method to produce 2-FDG for medical presence of $^{19}F_2$, the [^{18}F]fluoride can be obtained with very high specific activity (no-carrier-added), e.g., from the nuclear reaction of ^{18}O(p,n)^{18}F using an oxygen-18 (^{18}O) enriched water target (*13*). This reaction can be carried out with a small 10 MeV proton accelerator.

Three successful nucleophilic syntheses of 2-^{18}FDG are published. One based upon the replacement of the triflate group of methyl 4.6-*O*-benzylidene-3-*O*-methyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranoside by ^{18}F$^-$ (*10*) and the other on the reaction of [^{18}F]fluoride with methyl 4.6-*O*-benzylidene-2.3-*O*-sulfuryl-β-D-mannopyranoside (*11*). The substitution of the triflate-group proceeds with a yield of about 30%, but the difficulty in removing the methyl group from the 3-*O*-position reduced the overall yield significantly (~10%).

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[^{18}F]F_2 production was technically complex and required the addition of highly toxic and reactive fluorine gas. With [^{18}F]F_2, only a maximum 50% of the ^{18}F produced by the ^{20}Ne(d,α)^{18}F reaction could be incorporated into the final product; this synthesis also gave a mixture of isomers, reducing the overall yield. Fortunately, ^{18}F (as fluoride ion) could also be produced in far higher yields via the ^{18}O(p,n)^{18}F reaction than via the ^{20}Ne(d,α)^{18}F reaction. Production of ^{18}F also did not require the addition of fluorine gas (*4*). This set the stage for intense competition between different groups of chemists to produce ^{18}F-FDG via a nucleophilic displacement reaction with [^{18}F]fluoride ion. Several different nucleophilic routes were explored from 1976 to 1986 (*4*). However, similar to the electrophilic route, all were plagued with difficult steps, including low yields in the incorporation of ^{18}F and difficulty in removal of protective groups.

A major advance in the synthesis of ^{18}F-FDG from [^{18}F]fluoride was reported in 1986 when Hamacher and colleagues at the Kernforschungsanlage Jüulich reported that Kryptofix [2.2.2] (Merck), a phase-transfer catalyst, could be used to increase the reactivity of [^{18}F]fluoride in nucleophilic displacement reactions (*2*). The reaction of Kryptofix 222 [^{18}F]fluoride with 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-manno-pyranose gives 1,3,4,6-tetra-*O*-acetyl-2-[^{18}F]fluoro-β-D-gluco-pyranose with a 95% incorporation of ^{18}F. The overall synthesis, including purification, proceeds in about 60% yield. The synthesis is also technically simple. It involves two steps, displacement of a trifluoromethanesulfonyl group with ^{18}F with [^{18}F]fluoride and removal of the acetyl groups with HCl. This synthesis produces a single isomer (as confirmed by ^{19}F nuclear magnetic resonance of the product from the synthesis with unlabeled fluoride ion) and was an elegant solution to the need to produce ^{18}F-FDG in high yield and in high purity without added carrier.

Over the past three decades, considerable effort has been put into fine tuning the reaction, developing automated radiosynthesis modules, and identifying impurities and contaminants that are carried through to the final product (*4*). This need has become more critical with the increasing use of ^{18}F-FDG in clinical practice, where a pharmaceutical-quality product is required.

In summary, Hamacher's simple and elegant radiosynthesis has made ^{18}F-FDG available for distribution from many central production sites around the world for basic and clinical applications in institutions that have a PET (or PET/CT) scanner but no cyclotron or chemistry infrastructure. This radiosynthesis was transformative. ^{18}F-FDG is now used routinely by many hospitals as an off-the-shelf radiopharmaceutical for clinical research and diagnosis in heart disease, neurologic disorders, and oncology, which is the area of most rapid growth.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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ranging from 1 to 50 mCi of no-carrier-added [^{18}F]fluoride. TLC (MeCN:H_2O/95:5) of the FDG solution has shown that ~ 99% of the [^{18}F] fluorine was present as 2-^{18}FDG (Rf 0.37) whereas only 0.5 to 1% of the $^{18}F^-$ activity was located at the starting point. The TLC on monosodium phosphate impregnated silica plates as described by van Rijn et al. (*12*) makes it feasible to separate the epimeric sugars FDG and FDM. Using this modified TLC method, only one radioactive component with a Rf-value equivalent to that of FDG appeared to be present.

Additionally, the isocratic HPLC (Lichrosorb-NH_2 column) gave the same retention time for the radiochemical product and the authentic 2-FDG sample (HPLC retention time 3.9 min). As in the case of the TLC, radiochemical impurities were not detected.

The nucleophilic ^{18}F fluorination was also performed satisfactorily in anhydrous THF but the reaction time of 25 to 30 min was significantly longer than in the dipolar solvent acetonitrile (5 min).

CONCLUSION

The advantage of the synthetic method presented here is the high yield (max. 55% uncorrected) of no-carrier-added 2-^{18}FDG based on the phase-transfer mediated substitution of triflate by [^{18}F]fluoride. The stereochemical specificity of the nucleophilic displacement combined with a rapid hydrolysis of the acetylated sugar derivative makes it possible to synthesize epimerically pure 2-^{18}FDG with high specific activity. The synthesis of 2-^{18}FDG was carried out successfully with larger quantities of [^{18}F]fluoride suitable for clinical use. In addition, the precursor 1.3.4.6 tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranose can be easily prepared in a two step reaction starting with D-mannose.

FOOTNOTES

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