MINI-REVIEW

^{18}FDG Synthesis and Supply: a Journey from Existing Centralized to Future Decentralized Models

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Abstract

Positron emission tomography (PET) as the functional component of current hybrid imaging (like PET/CT or PET/MRI) seems to dominate the horizon of medical imaging in coming decades. ^{18}Flourodeoxyglucose (^{18}FDG) is the most commonly used probe in oncology and also in cardiology and neurology around the globe. However, the major capital cost and exorbitant running expenditure of low to medium energy cyclotrons (about 20 MeV) and radiochemistry units are the seminal reasons of low number of cyclotrons but mushroom growth pattern of PET scanners. This fact and longer half-life of ^{18}F (110 minutes) have paved the path of a centralized model in which ^{18}FDG is produced by commercial PET radiopharmacies and the finished product (multi-dose vial with tungsten shielding) is dispensed to customers having only PET scanners. This indeed reduced the cost but has limitations of dependence upon timely arrival of daily shipments as delay caused by any reason results in cancellation or rescheduling of the PET procedures. In recent years, industry and academia have taken a step forward by producing low energy, table top cyclotrons with compact and automated radiochemistry units (Lab-on-Chip). This decentralized strategy enables the users to produce on-demand doses of PET probe themselves at reasonably low cost using an automated and user-friendly technology. This technological development would indeed provide a real impetus to the availability of complete set up of PET based molecular imaging at an affordable cost to the developing countries.

Keywords: PET - ^{18}FDG - cyclotrons - nucleophilic production - microfluidics - decentralized production

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Introduction

Positron emission tomography (PET) has become the hallmark of nuclear medicine attributed to its high sensitivity, better spatial resolution and absolute quantification. This is due to ability of PET radionuclides to incorporate into biological molecules with subtle disruption of biological process of disease. Since its introduction in 1999, PET/CT hybrid imaging (or PET/MRI in recent years) has become standard of care primarily in oncology and also in cardiology and neurology (Alavi et al., 2004; Liu et al., 2013). In fact successful marriage between PET (functional) and CT or MRI (anatomical) modalities is the sentinel reason for this robust and accelerated application in clinical arena and its demand worldwide (Gambhir et al., 2001). A large number of Fluorine-18 (^{18}F), Carbon-11 (^{11}C) and Gallium-68 (^{68}Ga) labeled radiopharmaceuticals are being used for various clinical indications. But 18F labeled fluorodeoxyglucose (^{18}FDG) is the most commonly used PET radiopharmaceutical around the globe (Schmor, 2011) and some have also recommended it role in cancer screening (Ghotbi et al., 2007) In this technical note we will focus upon pharmacokinetics of ^{18}FDG, its synthesis, logistic pertinent to its supply and future overview.

^{18}Flourodeoxyglucose (^{18}FDG)

In 1976 at Brookhaven National Laboratory, Tatsuo Ido and Wolf Al and their team successfully produced ^{18}FDG and this step had provided a real impetus to PET imaging (Ido and Wolf, 1978). Dr. Abbas Alavi was the first nuclear physician who injected ^{18}FDG in two normal volunteers for brain imaging (Alavi, 2013).

^{18}FDG is a radiolabeled analog of glucose, in which the hydroxyl group on the 2-carbon of a glucose molecule is replaced by a fluoride atom. It competes with glucose for active transport from blood to cells by various type of specific facilitative glucose transport proteins (GLUT). Within the cell it is phosphorylated by hexokinase to FDG-6-phosphase (FDG-6-P) as the first step toward glycolysis. However, FDG-6-P cannot undergo further metabolism as

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it is not a substrate for further glycolytic pathways and effectively trapped intracellularly (Gallagher et al., 1978). This metabolic trapping of ^{18}FDG is the seminal reason of *in vivo* imaging and assessment of metabolic function. Malignant tumors have high avidity for glucose and enhanced glycolysis and have over-expressions of GLUT, especially GLUT1 and GLUT3. Importantly inflammatory tissues also have high expressions of GLUT1 (Mochizuki et al., 2001) leading to a false positive findings and diagnostic dilemma in clinical PET imaging (Chung et al., 2004). The degree of ^{18}FDG uptake correlates with expressions of GLUT1 which is likewise related to tumor grade in many tumor types (Tateishi et al., 2006) but not necessary all malignancies (Avril, 2004). Glucose metabolism in heart muscle, fat and skeletal muscle is mediated by GLUT4 which is insulin-dependent. It is imperative to be cognizant of expression and up-regulation of various GLUTs and activity level of hexokinase to understand basis of physiological, pathological and nuisance uptake of ^{18}FDG (Brown et al., 2002).

Biodistribution of ^{18}FDG in human body depends upon pattern of glucose metabolism in various organs. High ^{18}FDG uptake is seen in brain and urinary tract. Since ^{18}FDG unlike glucose is not reabsorbed by renal tubules, approximately 20% of the administered dose is excreted unchanged within the first 2 hours after administration (Thomson, 2003). Areas of consistent uptake of intermediate intensity are liver, spleen, thyroid and bone marrow (in patients without drugs or conditions that would potentially stimulate bone marrow activity). Other areas which may show physiological uptake are salivary glands, lymphoid tissues in the head and neck, thymus (especially in children), lactating breast and areola, uterus (during menses), GI tract, and skeletal and smooth muscle (Delbeke et al., 2006). Visualization on myocardial ^{18}FDG uptake in oncological imaging exhibits a large degree of unexplained intra- and inter-subject variability most likely the result of varying levels of insulin present or some specific cardiac disorders (Fukuchi et al., 2007).

Synthesis of 18FDG

^{18}FDG synthesis is a multi-stage process that begins with production of radioactive ^{18}F (a positron emitting radionuclide) in a cyclotron. Radioactive ^{18}F can be produced in cyclotron by either electrophilic ^{18}Fluorine ($^{18}F_2$) or nucleophilic ^{18}Fluoride (^{18}F-) followed by two different processes to synthesize ^{18}FDG as electrophilic fluorination and nucleophilic substitution respectively. ^{18}FDG at Brookhaven National Laboratory in 1976 was synthesized by electrophilic fluorination using neon gas target with 0.1-1% of fluorine gas via ^{20}Ne (d,α) 18FDG reaction (Fowler and Ido, 2002). The major limitations of this approach are low yield (8%), long synthesis time (2 hour) and incorporation of only 50% of 18FDG into precursor molecule (Triacetylglucal) (Casella et al., 1980; Fowler and Ido, 2002). In nucleophilic fluorination, ^{18}F- is produced by bombarding ^{18}O enriched water (^{18}O(p, n)^{18}F-) followed by substitution reaction in precursor Mannose Triflate in presence of a catalyst Kryptofix222™ and acetonitrile as solvent (Hamacher et al., 1986). This method was introduced by Hamacher et al (1986) and has a consistent yield of over 65% and shorter synthesis time of 50 min (www-pub.iaea.org/MTCD/publications)[1]. Due to these facts, nucleophilic method using ^{18}O(p, n)^{18}F is the current method of choice for ^{18}FDG synthesis.

Cyclotrons

The robust growth of PET imaging over the last two decades has been associated with exemplary growth in cyclotron industry as these particle accelerators provide positron emitting isotopes. It was E Lawrence who invented the first cyclotron in 1930 (Lawrence and Edlefson, 1930) and in last 80 years phenomenal growth has been observed in design and functioning of cyclotrons. Currently various types of cyclotrons are available like negative ion accelerating cyclotron, positive ion accelerating cyclotron, superconducting cyclotron, low energy linear accelerator and electrostatic accelerators (Schmor, 2011). However, due to higher yield and lesser running cost, negative ion cyclotrons are commonly used in health sector. The cyclotrons can also be classified according to proton energies: *(a)* <20 MeV cyclotrons are primarily used for production of positron emitting radionuclide; *(b)* cyclotrons with 20-35 MeV which can produce gamma emitting isotope as well as positron emitting radionuclide and *(c)* cyclotrons >35 MeV proton energies which are used to produce isotopes for therapy purposes (Schmor, 2011). According to an IAEA 2006 report, about 50% of cyclotrons worldwide are less than 20 MeV and about 75% are being used for 18FDG production (IAEA Tech. Rep. IAEA-DCRP, 2006).

Centralized Production of 18FDG other PET Probes

Short half-life of positron emitting radionuclide (like ^{15}Oxygen=2 minute, ^{11}Carbon=20 minutes, ^{13}Nitrogen=10 minutes, etc.) demands an onsite cyclotron facility. But capital cost, infrastructure and high ongoing personnel and operating costs of these cyclotrons are the major reasons of their non-existence in every PET/CT facility. However, longer half-life of ^{18}FDG (110 minute) allows time for complex synthesis or delayed imaging and it can be transported to other PET facilities placed at significant distances (Schlyer, 2004). In this centralized model, ^{18}FDG is produced by commercial PET radiopharmacies and dispensed the finished product (multi-dose vial with tungsten shielding) to customers having PET imaging services by special vehicle or by air. This model has been successfully practiced in many countries as spreading the ^{18}FDG production cost over many customers has made it affordable and accessible to these users. A batch of ^{18}FDG can be increased by simply changing the amount of the radioactive isotope at the beginning of synthesis, a function of the bombardment time in the cyclotron with no change in the synthesis, purification, and quality control (QC) steps. However, the disadvantage of this centralized model is total dependence on timely arrival of daily shipments as delays due to any reason results in rescheduling or cancellation of procedures and

inconvenience to patients and imaging service providers.

Future Prospects (Decentralized Production of 18FDG and other PET Probes)

Continuous research and recent developments in PET radiopharmacy has opened a new vista of decentralized approach. This enables the users to produce on-demand doses of PET probe themselves at a reasonably low cost using an automated and user friendly technology. This concept has been materialized by Advanced Biomarker Technology (ABT Molecular Imaging, Inc) which has introduced a 7.5 MeV, small table-top cyclotron to produce single patient doses of ^{18}F (and ^{11}C in future). This system is interfaced with a compact, self-shielded and automated radiochemistry module dispensing ^{18}FDG dose on demand (http://advancebiomarker.com). To excel decentralized production, new technologies and automation are needed that simplify tracer production, reduce cost, size and complexity of equipment required, and eliminate the need for highly skilled radiochemists in routine tracer production. Already marketed kit-based radiosynthesizers and upcoming microfluidic technologies (Lab-on-Chip) will enhance the benefits of decentralized production of PET probes on demand by users themselves (Schmor, 2011). This technological development would indeed provide a real impetus to the availability of full-fledged PET based molecular imaging at an affordable cost to the developing countries.

^{18}FDG is the most commonly used PET probe around the globe with countable production facilities nourishing a large number only-PET imaging facilities (centralized approach). However, recent developments on technological frontiers have produced low energy, table-top and small foot print cyclotrons with compact and fully automated radiochemistry module with microfluidic technology (Lab-on Chip). This decentralized approach would enable the users to produce on-demand dose of PET probes by themselves at reasonably low cost by acquiring these compact, automated, relatively low cost and user friendly units.

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