18F-FDG Imaging: Molecular or Functional?

Molecular imaging in oncology is defined as the noninvasive imaging of the key molecules and molecular-based events that are fundamental to the malignant state. By this definition, there is no doubt that 18F-FDG PET imaging is molecular imaging.

The biologic basis for 18F-FDG PET in oncology is the Warburg effect (1). Technically, this is an increase in glycolysis under aerobic conditions and is characteristic of the malignant state. FDG is an analog for glucose and is taken up by the cell on glucose transporters and phosphorylated by hexokinase to the glucose-6 phosphate. The FDG-6P is not a good substrate for further enzyme action by more distal enzymes of the glycolytic chain. Glucose-6-phosphate can be broken down by glucose 6-phosphatase, but this enzyme is markedly downregulated in cancer cells.

Those of us in nuclear medicine owe a debt of gratitude to Louis Sokoloff and his colleagues, who developed the deoxyglucose method for measuring cerebral glucose metabolism in the brains of living animals (2). The development of FDG and an understanding of the ways in which this could be adapted to noninvasively measure brain glucose in humans represent a cardinal advance in the study of human brain physiology and tissue biochemistry in general (3). The adaptation of these methodologies to tumors began with the work of Di Chiro et al. (4) at the National Institutes of Health.

The biochemical reasons for the acceleration in glucose metabolism in cancer cells are beginning to come to light, and, in general, activated glucose metabolism is clearly a central component of the malignant phenotype, which is influenced by many changes in the cell (5, 6). These changes include upregulation of glucose transporters (7); a manifold increase in hexokinase activity associated with redistribution of the hexokinase enzyme within the cell with binding to mitochondria outer membranes (8); oncogenic transformation with src, ras, and c-myc, along with certain growth factors (9); and HIF1α activation and expression (10). The protein kinase Akt, a signal transduction protein with multiple functions, along with proteins down the signal cascade pathway, such as mTOR, appear to be at the hub of control of the metabolism of glucose as well as other nutrients within the cell (11).

Now and for some time in the future, 18F-FDG PET imaging will be the poster child for molecular imaging, at least in oncology. More than 1 million patients per year are imaged with 18F-FDG PET in the United States alone. Reimbursement is available for imaging and assessment of 10 common tumors. Recent reviews have appeared with new data on efficacy and applications (1). Current clinical uses for 18F-FDG PET imaging reflect the breadth of clinical applications that will no doubt be expanded in the near future. These include: staging extent of common tumors, detecting recurrence, treatment planning in radiation oncology, aiding prognosis development, and monitoring treatment response via biomarker imaging.

Topical Questions

Although widely useful, 18F-FDG has limitations. What is “beyond FDG?” It is likely that 18F-FDG will continue to be the backbone of PET for some time to come. 18F-FDG will be the first study performed in many patients. For circumstances in which good results cannot be obtained with this tracer, additional, more specific tracers will be employed. I believe that antibodies labeled with positron emitters will be an important part of the solution for many of the defects of 18F-FDG. In oncology, one of the problems with 18F-FDG is the specificity issue—that is, uptake may be related to tumors and their accelerated metabolism or it may be the result of inflammatory conditions. Antibodies offer the potential of antigen-specific targeting, which may be helpful in many circumstances by providing specific information about the tissue type that is causing the abnormality.

My view is that a second large group of imaging procedures that will be used in oncology PET will involve radiolabeled drugs. Individual variations in metabolism of important pharmaceuticals account for a wide variation in side effects and response. Although it is still a hypothesis, it is my view that knowledge about the distribution of these important drugs will provide important insights into the potential for good or ill that will accompany their use in specific patients.

18F-FDG also has limitations in determining tumor response. I see the development of another class of drugs that will deal with the pharmacodynamics of treatment response. It is now known that drugs may affect specific molecules within the cell as a basis for their effect. Imaging modalities that will quantify the effects of these targeted therapies on the specific molecules will also be widely used. In some cases, the pharmacodynamic effects will be illustrated by changes in metabolism. It is likely that a drug such as fluorothymidine FLT will be very useful as an adjunct to FDG in monitoring treatment response. This is because of the tight association between FLT and proliferation, which is often affected by anticancer therapies.

Because most PET imaging is performed in combination with CT, should 18F-FDG and other molecular imaging agents simply be considered as another form of contrast?
It is true that much PET imaging will be performed by radiologists in private practice who may or may not be interested in the underlying mechanisms whereby pharmaceuticals are concentrated or, indeed, what underlies the specific application to individual disease types. In one way it is a good thing that this is true, because completely trained individuals such as nuclear medicine physicians are not numerous enough to meet the demand for the rapidly expanding applications that we foresee with PET/CT. However, the academic disciplines of imaging require its clinician scientists and expert specialists to understand the underlying biochemistry and the ways in which it might be applied to assist in the management of patients. In order to develop new methodologies and new molecular imaging methods, a well-trained cadre of individuals will be needed with a greater depth of understanding of molecular medicine as it applies to imaging.

REFERENCES


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Molecular Imaging: A Tool for Developing Central Nervous System Drugs

Over the last decade, large drug companies have developed an interest in imaging, particularly with regard to the evaluation of drugs affecting the central nervous system (CNS). As an example of this application, Merck & Co., Inc. has created an imaging division with more than 90 employees and multiple high-level instrumentation foci, including PET/CT, SPECT/CT, MR imaging, and MR spectroscopy. The main focus of this program is on CNS drug development for use in animals and humans. The rationale and application of these development efforts have been described in several publications (1–5).

Topical Questions

Alzheimer’s disease affects a large proportion of the population. What is the role of imaging in evaluating Alzheimer’s disease and in the development of new CNS-based drugs? In particular, what is the role for agents (such as 18F-PIB) that specifically image beta amyloid deposits?

As part of the July 2006 issue of Nature Medicine, a group of 32 experts gave their opinions about advances that were important to an understanding of Alzheimer’s. In a summary article on “Pinpointing plaques with PIB,” Kaj Blennow and Henrik Zetterberg discussed possible applications for imaging beta amyloid aggregation in the brain. Among the potentially useful applications would be differentially identifying the first clinical phase of Alzheimer’s disease from isolated memory dysfunction (mild cognitive impairment [MCI]). About 40%–60% of individuals with MCI will develop full-fledged Alzheimer’s disease. Although some individuals with MCI may have increased uptake of PIB, stratifying patients according to the degree to which they have PIB uptake may be a way to differentiate a population likely to develop Alzheimers disease. This would be useful for testing drugs that may have potential in Alzheimer’s disease.

We now know individuals may have distinct metabolic patterns for key enzymes affecting dopamine metabolism, such as monoamine oxidase inhibitors, and that these differences may play a role in addiction. Do individual variations in metabolism play major roles in other neurotransptic drugs, and have PET and MR imaging facilitated a better understanding of the chemical basis for common mental illness and neurologic dysfunction? In developing