NEWSLINE Commentary

Revealing Biochemistry in a Single Image

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Nuclear medicine is a medical specialty that uses the nuclear properties of radioactive and stable nuclides to evaluate metabolic, physiologic, and pathologic conditions of the body. It evaluates the biochemistry (i.e., metabolism) and physiology of normal and abnormal tissue. The definition of nuclear medicine does not include the evaluation of anatomy but, rather, focuses on function.

Most radiopharmaceuticals currently used in nuclear medicine evaluate tissue blood flow. These radiopharmaceuticals include: ^{201}Tl-chloride and ^{99m}Tc-sestamibi for myocardial perfusion imaging; ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 for renal imaging; and ^{99m}Tc macroaggregates of albumin for pulmonary perfusion imaging. With several recent advances, nuclear physicians are now able to use radionuclides to measure biochemical processes. These tracers present a challenge as well as an opportunity to the specialty as a whole. They are still perceived as being too complex and not readily available on a widespread basis.

Many practitioners are wondering if these radiopharmaceuticals will be broadly disseminated or if their use will be restricted to regional university medical centers. Some feel that the procedures for evaluating biochemical processes are too complex to be performed in a community hospital because data acquisition and processing require complicated models, arterial blood sampling and quantitative imaging. While these issues are valid, I believe that the information provided by scans that measure biochemical processes will become a vital part of nuclear medicine and will thus be offered in all centers performing nuclear medicine.

The Three Biochemistry Tracers

Three radiopharmaceuticals are now available for biochemistry imaging, and they can determine information (such as receptor status and glucose metabolism) from a single image. Indium-111-pentetreotide localizes in somatostatin receptors. Iodine-131- or [^{123}I]metaiodobenzylguanidine (MIBG) accumulates in tissue related to the uptake-1 and vesicular storage mechanisms. Fluorine-18-2-fluorodeoxyglucose (FDG) reflects glucose metabolism after its administration.

Human somatostatin is a 14 amino-acid-long peptide hormone that is present in the hypothalamus, cerebral cortex, brainstem, gastrointestinal tract and pancreas. The biologic half-life of human somatostatin is only 2 to 4 minutes. Indium-111-pentetreotide has a biologic half-life of 2 hours, and images of somatostatin receptor distribution are obtained 24 and/or 48 hours after administration. Localization of the tracer in these receptors can be demonstrated by planar or SPECT imaging.

Radioiodinated MIBG localizes in cells that have uptake-1 and vesicular storage mechanisms. MIBG is used to characterize neuronal uptake mechanisms of the myocardium in a single image. Many neuroendocrine tumors also have uptake-1 and vesicular storage mechanisms. Carcinoid tumors and pheochromocytomas are two neuroendocrine tumors that commonly accumulate MIBG. In addition to imaging the distribution of tracer accumulation 24 hours after administration, [^{131}I] MIBG can be used in large doses (200 to 300 mCi) to effectively treat tumors that accumulate MIBG.

FDG, on the other hand, behaves in a manner similar to that of glucose. It is transported across the capillary membrane into tissue and is phosphorylated to FDG-6-phosphate by hexokinase. Once it is phosphorylated, however, it is metabolically trapped in the cell and undergoes no additional metabolization. Quantification of glucose metabolic rates can be obtained using FDG and PET. The formula for quantification of glucose metabolic rate comprises several parameters: the plasma glucose level, total regional ^{18}F, free FDG in the region, the lumped constant, which is a calibration term related to the fact that glucose and FDG are not identical, and total FDG delivered to the region (arterial input function). These parameters are all relatively easy to obtain if quantified glucose metabolic rates are wanted. For clinical procedures now being performed in nuclear medicine, however, quantification of glucose metabolic rate is usually not necessary.

FDG and Tumor Imaging

In 1931, the biochemist Otto Warburg reported that tumor cells avidly metabolize glucose and produce lactic acid. Warburg initially hypothesized that glucose was a cause of tumor development. More recently, Louis Sokoloff and colleagues developed the autoradiographic methodology and models for quantifying glucose metabolic rates using ^{14}C-2-deoxy-D-glucose. Many important developments in understanding the brain have resulted from the use of this technology. Shortly after the development of autoradiographic methodology and models by Sokoloff and colleagues, Al Wolf and colleagues at Brookhaven National Laboratory synthesized FDG, which has been used increasingly since the late 1970s.

Initial studies using FDG focused on its applications in the brain and heart, but recent studies have demonstrated its utility in evaluating tumors. Three methods have evolved in evaluating images obtained in patients with suspected tumors. Visual image analysis is performed at a fixed time after FDG administration. The second method is semiquantitative analy-

sis, which may also be performed using a standardized uptake (SUV) ratio; however, a region of interest (ROI) ratio is also used. The FDG SUV is calculated similar to that for thyroid uptake. (It is determined by the activity in a ROI divided by the administered dose per body weight.) The third method of evaluating FDG images is quantitative measurement of glucose metabolic rate.

Giovanni DiChiro and colleagues at the National Institutes of Health first demonstrated the utility of FDG imaging in brain tumors. They demonstrated that low-grade tumors have a lower metabolic rate than high-grade tumors. Low-grade tumors such as astrocytomas and oligodendrogliomas have rates lower than normal white matter. High-grade tumors such as anaplastic astrocytomas and glioblastoma multiforme have rates greater than those for white matter. The NIH researchers also demonstrated that visual assessment of glucose metabolic rates is more accurate than quantitative assessment. In a 1988 editorial that DiChiro co-authored, he concluded: "As for clinical diagnosis, surely Lord Kelvin himself, a practical man who was knighted for introducing the telephone into Great Britain, would see the need to abandon quantitation when not appropriate to the task at hand."

More recently, FDG-PET imaging has been used to characterize a variety of other malignancies. FDG has been found to accumulate not only in primary lesions, such as in lung carcinoma, but also in metastatic lesions such as mediastinal nodal metastases and adrenal metastases. The FDG-PET scan is quite accurate in characterizing a radiographically indeterminate solitary pulmonary nodule as benign or malignant. In a study of 51 patients with indeterminate solitary pulmonary nodules reported by Ned Patz et al. from Duke University Medical Center, FDG-PET studies had a sensitivity of 100% and a specificity of 89%. Val Lowe and colleagues from Duke subsequently reported that qualitative analysis of the images was equally accurate to semiquanitative methods of image analysis. Thus, FDG is quite accurate in characterizing various malignancies such as lung cancer. Visual analysis of the images obtained 60 minutes postinjection is appropriate for image analysis.

A New Alternative to PET

PET imaging is presently limited to approximately 60 medical centers in the United States. Many centers are using FDG with systems other than typical PET scanners. Gamma cameras have been fitted with specially designed high-energy collimators which image the annihilation radiation from FDG. For example, Martin Sandler, MD, and colleagues at Vanderbilt University have demonstrated that FDG imaging can be performed using a camera fitted with a high-energy collimator. They combined myocardial perfusion imaging using ^{99m}Tc-sestamibi with FDG imaging in a protocol that evaluates myocardial ischemia. They have also used FDG-SPECT to detect tumors. In addition, several centers have demonstrated the feasibility of FDG and gamma camera imaging. During the next year, we are going to see a spectrum of technology used to image positron-emitting radionuclides. We are already witnessing the development of dual-head gamma cameras with coincidence circuitry for imaging FDG.

In the early 1970s, Gerd Muellehner and colleagues at Nuclear Chicago attempted to image annihilation radiation with a dual-head gamma camera using coincidence circuitry without collimators. Although they were unsuccessful in developing a clinically practical imaging system at the time, several advances in the electronics of gamma cameras have now made this technique feasible. A dedicated sodium iodide detector PET system has been manufactured and is less expensive than the state-of-the-art bismuth germanate systems with two-dimensional and three-dimensional acquisition capabilities.

Although these new techniques for FDG imaging can provide excellent information concerning glucose metabolism, they have several caveats. Alan Fischman and colleagues at Massachusetts General Hospital defined some potential problems with biochemical evaluation in a single image. In an article in *The Journal of Nuclear Medicine* (J Nucl Med 1994; 35:1308-1312), they concluded that the complex information portrayed in the image by the SUV is an oversimplification of glucose metabolism. Since FDG reflects glucose metabolism, the amount of FDG accumulating in the area of interest may be decreased if the serum glucose level is elevated.

Another factor which is not adequately characterized for all tumors is the lumped constant. If tumor cells differentiate between glucose accumulation and FDG significantly, this difference could greatly alter the image.

One obvious factor that will determine widespread application of FDG in community hospitals is its availability. The Food and Drug Administration recently announced its policy requiring all facilities producing FDG to obtain a New Drug Approval (NDA) and/or have a PET Review Committee. Currently, most facilities in the U.S. produce FDG under the authority of their State Board of Pharmacy. Most will find it quite difficult to manufacture FDG under an NDA because of the FDA requirements that FDG be made using current good manufacturing practice standards.

In conclusion, a single image can indeed represent biochemistry. Some examples of imaging biochemistry are the demonstration of somatostatin receptor sites using ^{111}In-pentetreotide, the distribution of uptake-1 and vesicular storage mechanisms using ^{131}I-or [^{123}I]MIBG, and the determination of glucose metabolism using FDG. Qualitative, semiquanitative and quantitative techniques are available for evaluating FDG images. Improvements in gamma camera technology will permit the widespread utilization of high-energy imaging of radiopharmaceuticals such as FDG. This promise offers exciting opportunities for nuclear medicine.

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