INVITED COMMENTARY

Improving Amino Acid Imaging: Hungry or Stuffed?

With the increasing clinical application of FDG PET, interest in metabolic imaging in general is growing among clinicians. The reasons for the great impact that FDG PET is currently making in oncologic diagnostics are (a) the exceptionally high uptake and trapping of FDG in malignant cells and (b) the technical performance of PET systems with high resolution and counting efficiency. These 2 factors together lead to a detection level that just reaches clinical relevancy and may surpass other modalities in tumor staging (*1*). In other words, small lesions (approximately 1 cm) can be detected with a reliability that is adequate as a basis for clinical decisions. Any concession in one of these factors reduces clinical possibilities.

The increased anaerobic glycolysis in tumor tissue is the target for the uptake of FDG (*2*). Unfortunately, this mechanism also generates considerable uptake in macrophages and inflammatory cells (*3*,*4*). This limits the tumor specificity of FDG and, therefore, positive PET scans frequently require further confirmation. Especially in the field of nuclear medicine, a continued search for better tracers is going on, as a side effect of the FDG boom. Radiolabeled amino acids and also ^{18}F-fluorodeoxythymidine (FLT) and ^{11}C-choline are examples of tracers aimed at other metabolic targets, such as the increased protein metabolism, DNA synthesis, and membrane synthesis, respectively (*5*–*7*). Some of these alternative tracer methods are indeed less troubled by interfering uptake in inflammatory tissue (*5*). However, usually they violate the first success factor of FDG, because uptake of these alternative tracers in tumor cells appears to always be lower than FDG uptake. Violations of the second factor, such as the use of gamma cameras with coincidence detection, also prevent such methods from generating true clinical impact (*8*,*9*).

Although this type of reasoning appears correct at first glance, PET is still not available everywhere, and if uptake of a tracer is high enough, tumor lesions can be detected, even with the lower resolution of SPECT systems. It may not be problematic that the low resolution may blur 2 small lesions into 1, as long as they are detected. Therefore, the main point is to find a tracer with high specific uptake in tumor tissue (*1*) and to look for methods to improve tumor uptake or contrast with background (*2*). The class of artificial amino acids tracers such as 3-^{123}I-iodo-L-α-methyltyrosine (3-IMT) and ^{18}F-fluoroethyltyrosine (FET) is promising in this field. Initial results of imaging methods using these tracers appear to be slightly below the required detection level for small lesions. However, remarkable results have been reported with 3-IMT uptake, even with SPECT systems, in brain tumors, head-and-neck cancer, lung cancer, and sarcoma (*10*–*16*). Better performance is to be expected with FET PET (considered the most promising second oncology tracer by Henry Wagner, Jr., at the 48th Annual Meeting of the Society of Nuclear Medicine, Toronto, Ontario, Canada, June 23–27, 2001), and clinical studies are eagerly awaited. In this issue of *The Journal of Nuclear Medicine*, Lahoutte et al. (*17*) focus on methods to further improve imaging using artificial amino acids. They focused on 3-IMT but correctly suggest that the results may also apply to the PET variants such as FET (*18*). If improvement in tumor uptake and contrast can indeed be obtained, the detection limit of FET PET, for example, may reach clinical significance and compete with and complement FDG imaging.

How can tumor uptake of amino acids be manipulated and improved? Lahoutte et al. (*17*) are the first to suggest that the fasting state in which patients are usually studied may not be optimal. It is remarkable that this simple issue has hardly been studied, also for the newer metabolic tracers. They base their observations on a R1M rhabdomyosarcoma model in rats. Baseline images in fasting state were compared with images obtained after preloading with a single amino acid. They found increased tumor uptake after preload and increased contrast. Tumor uptake was nicely corrected for blood-pool activity and background activity, although they do not provide (essential) details on their method for region-of-interest definition. The highest increase in tumor uptake was found after preloading with tryptophan (+36%), although the increase in tumor contrast with background—which determines detectability—was lower (+11%). This increased uptake is in agreement with the specific affinity of tryptophan for amino acid transport system L, which is responsible for uptake of aromatic amino acids in virtually all species (*19*,*20*). It has been shown by multiple investigators that 3-IMT and FET also use this system L to enter (tumor) cells (*21*–*24*). At first glance, one

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For correspondence contact: Pieter L. Jager, MD, PhD, Department of Nuclear Medicine and PET Center, University Hospital Groningen, P.O. Box 30001, Groningen, 9700 RB, The Netherlands.
E-mail: p.l.jager@nucl.azg.nl

would expect decreased uptake after administration of an excess of unlabeled substrate, as is indeed the case for another important transport system, the sodium-dependent system A. Starving cells increase tremendously their capacity to take up A-type amino acids, such as alanine (*25*). However, for system L–transported amino acids everything appears to be different. An important phenomenon in the complex regulation of these amino acids is called "trans-stimulation," in which the intracellular concentration of 1 type of amino acid stimulates uptake of another type. In addition, system L is also involved in efflux of various types of amino acids from the cell ("countertransport") (*19*,*20*). An L-type amino acid may be transported into the cell, and an A-type amino acid can be extruded. In this way, preloading the cell with amino acids may increase the uptake of L-amino acids. Using this reasoning, the preloading amino acid does not have to be an L substrate itself, and the finding by Lahoutte et al. that especially L substrates increase system L activity is not necessarily expected. One could also reason that the fasting state increases system A activity, which leads to more system A substrates intracellularly, followed by increased efflux through the L system, which is finally associated with increased uptake of L substrates. In addition, other functional relations and connections between other transport systems may exist, apart from important regulatory factors such as glucocorticoid, insulin, and glucagon levels (*19*,*20*,*25*). Another issue in the interpretation of the findings of Lahoutte et al. is the precise concentration of amino acids required for trans-stimulation, rather than competitive inhibition. The latter phenomenon may have been dominant in the experiments by Langen et al. (*26*) in which competitive inhibition in brain and brain tumor uptake of 3-IMT were observed in humans after large doses of a cocktail of amino acids. Lindholm et al. (*27*) found decreased ^{11}C-methionine uptake in 5 patients after food ingestion, but methionine is generally not transported exclusively through the L system.

It is clear that the kinetics of amino acid metabolism and especially the efflux mechanisms are far more complicated than the uptake mechanisms of FDG, for example. Whatever the precise mechanism may be, the observed improvement in amino acid imaging in a nonfasting state is important and should be studied further intraindividually in humans. That patient preparation and interventions may considerably improve amino acid imaging is also illustrated by the increased tumor uptake of ^{11}C-5-hydroxytryptophan in neuroendocrine tumors, observed by the group from Uppsala (*28*). They observed a 3-fold increase in tumor uptake after administration of carbidopa. This is presumably caused by inhibition of peripheral metabolism (decarboxylation), which leads to prolonged and higher exposure of the tracer to the tumor.

As knowledge on methods to influence tumor uptake is expanding, the automatic assumption that "hungry" is better than "stuffed" may require correction. Who likes to be hungry anyway?

Pieter L. Jager, MD, PhD
PET Center
University Hospital Groningen
Groningen, The Netherlands

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