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The Potential of Metabolic Imaging

Valentina Di Gialleonardo, PhD,* David M. Wilson, MD, PhD,† and Kayvan R. Keshari, PhD*

Metabolic imaging is a field of molecular imaging that focuses and targets changes in metabolic pathways for the evaluation of different clinical conditions. Targeting and quantifying metabolic changes noninvasively is a powerful approach to facilitate diagnosis and evaluate therapeutic response. This review addresses only techniques targeting metabolic pathways. Other molecular imaging strategies, such as affinity or receptor imaging or microenvironment-dependent methods are beyond the scope of this review. Here we describe the current state of the art in clinically translatable metabolic imaging modalities. Specifically, we focus on PET and MR spectroscopy, including conventional ^{1}H- and ^{13}C-MR spectroscopy at thermal equilibrium and hyperpolarized MRI. In this article, we first provide an overview of metabolic pathways that are altered in many pathologic conditions and the corresponding probes and techniques used to study those alterations. We then describe the application of metabolic imaging to several common diseases, including cancer, neurodegeneration, cardiac ischemia, and infection or inflammation.
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Introduction

Metabolism refers to a set of enzyme-catalyzed biochemical reactions that take place within cells to maintain homeostasis. These reactions are organized into metabolic pathways, which are finely regulated by enzyme concentrations and catalytic efficacy as well as cofactor concentrations. In the clinic, several noninvasive imaging techniques have been developed to identify altered metabolic pathways characteristic of a variety of diseases.

PET and proton MR spectroscopy (^{1}H-MRS) represent most of the current noninvasive imaging techniques used to follow metabolism in vivo. With PET, it is possible to visualize the accumulation of radioactive molecules in a specific tissue or organ, with the anatomical location confirmed using coregistered CT or MRI. The most widely used PET metabolic probe has been ^{18}F-FDG, which is accumulated in highly glycolytic tissues. The main advantages of PET are that it is easy to perform, incredibly sensitive, and provides reasonable spatial resolution (approximately 5 mm isotropically for PET), although it suffers from lack of specificity due to the inability to resolve different radioactive molecules noninvasively. MR spectroscopy imaging (MRSI), like PET, is a technique that allows the detection of metabolites spatially resolved in vivo, but without the use of ionizing radiation. For example, for brain MRSI, using long echo time it is possible to visualize choline (Cho) used to evaluate membrane turnover and proliferation, creatine (Cr) for tissues energetics, N-acetylaspartate (NAA) for mitochondria and neuronal integrity, and lactate for anaerobic metabolism. Using short echo time, it is possible to identify additional metabolites such as myoinositol, glutamate, glutamine, and glycine. ^{1}H MRSI can be obtained in 10-15 minutes and, is therefore, easily incorporated into a routine imaging clinical study, minimizing discomfort to the patient.[1,2] One of the limitations of this technique is low sensitivity, with metabolite concentrations required to be on the order of mM (Fig. 1).

For the most part, patient MRS examinations have used ^{1}H, though despite technical challenges, there has also been considerable interest in using ^{13}C magnetic resonance spectroscopy imaging (^{13}C MRSI) to study the backbone of organic compounds in specific tissues. The MRI-detectable nucleus ^{13}C accounts for only 1.1% of molecular carbon and thus renders thermal equilibrium ^{13}C MRSI limited for rapid study of endogenous ^{13}C. To increase sensitivity and increase

*Department of Radiology and Molecular Pharmacology and Chemistry Program, Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY.

†Department of Radiology and Biomedical Imaging University of California San Francisco (UCSF), San Francisco, CA.

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Address reprint requests to Kayvan R. Keshari, PhD, Department of Radiology and Molecular Pharmacology and Chemistry Program, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065. E-mail: rahimikk@mskcc.org

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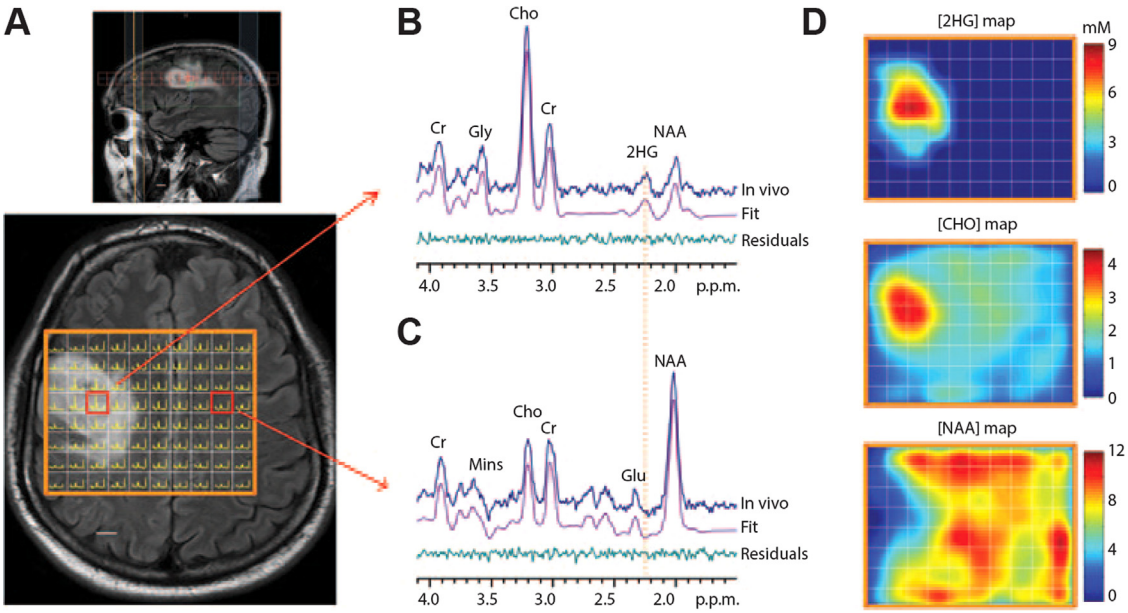

Figure 1 Spectroscopic imaging of 2HG. Routine long-echo 1H MRS in brain tumors is frequently used to study glial neoplasms, with associated alterations in choline, creatine, NAA, and lactate. In this case, a spectral editing technique was used to uncover the oncometabolite 2HG, which is a biomarker for IDH1 mutant status in low-grade glial neoplasms. (A) Multivoxel imaging spectra from a subject with a WHO grade 3 oligodendroglioma are overlaid on the T_2w-FLAIR image. The grid size is 1 × 1 cm^2, with slice thickness of 1.5 cm. The spectra are displayed between 4.1 and 1.8 ppm (left to right). (B and C) Two representative spectra (one from the tumor and another from the contralateral normal brain) are shown together with LC model fits and residuals. Mins, myoinositol. (D) The estimated concentrations of 2HG, choline, and NAA in individual voxels were color coded for comparison. The NAA level in gray matter in normal brain was assumed to be 12 mM. Scale bars, 1 cm. (Adapted from Choi et al.[142])

spectral resolution, isotopically enriched molecules are infused and ^{13}C spectroscopy is performed, often with ^{1}H decoupling.[3-5] These enriched compounds are virtually identical to the parent compound and typically provide no appreciable isotope effect in the time scale of the experiment. Infusions can increase the concentration of ^{13}C upward of 10^3-10^4 folds and therefore the metabolism of these molecules may be studied without background contamination of endogenous pools.[6] In contrast with PET, which can quantify the dynamic flux of radioactive probes over time, the most widely implemented MRS methodologies estimate metabolite concentrations at steady state.[7]

Another emerging noninvasive technique that is rapidly growing as a molecular imaging methodology is hyperpolarized MRI (HP MRI). HP MRI allows the detection of ^{13}C-enriched molecules with a signal increased several orders of magnitude (up to 10^7) in comparison with conventional spectroscopy. With this technique it is possible to follow single and multiple metabolic pathways using a single HP probe or a combination of several HP probes.

The great advantage of this technique is that after the injection, it is possible to follow in real time the conversion of a substrate to its metabolic products, whereas PET can detect only the incorporation of radiolabeled probes in a tissue without distinguishing the parent compound from the formed radiolabeled product.[8,9] HP MRI could, then, overcome the limitations of conventional ^{1}H and ^{13}C MRSI and provide complementary information to that from PET studies in the future.

In the following sections, the main metabolic pathways with respective probes designed to target those pathways are described in detail.

Glycolysis

Glycolysis is a 10-step metabolic pathway that takes place in the cytosol of cells and predominantly oxidizes glucose to pyruvate, resulting in increased adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide hydride (NADH).[10] Glucose is taken up from a range of glucose transporters, comprising 14 isoforms with specific expression pattern, substrate specificity, and kinetics.[11,12] In mammalian cells, after entering the cell, glucose is typically converted by hexokinase to glucose-6-phosphate (G6P). G6P has the potential to then continue into the glycolytic pathway, ending in the formation of pyruvate or it can leave glycolysis and enter the pentose phosphate pathway, which is essential for the regulation of the redox status as well as ribose synthesis. Glycolysis can also be altered in several pathologic conditions and targeting cellular transport and early metabolism has been the subject of extensive PET and MRSI research. ^{18}F-FDG-PET is a powerful clinical tool able to evaluate the upstream glycolytic pathway noninvasively. ^{18}F-FDG is transported efficiently into the cells by glucose transporters and in the cytosol is phosphorylated by hexokinase II to ^{18}F-FDG-6-phosphate and is trapped in the cell. ^{18}F-FDG-6-P can be dephosphorylated by G6P and then released into the extracellular space (Fig. 2).[13] This tracer has been used successfully