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The use of hyperpolarized carbon-13 magnetic resonance for molecular imaging☆

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ABSTRACT

Until recently, molecular imaging using magnetic resonance (MR) has been limited by the modality's low sensitivity, especially with non-proton nuclei. The advent of hyperpolarized (HP) MR overcomes this limitation by substantially enhancing the signal of certain biologically important probes through a process known as external nuclear polarization, enabling real-time assessment of tissue function and metabolism. The metabolic information obtained by HP MR imaging holds significant promise in the clinic, where it could play a critical role in disease diagnosis and therapeutic monitoring. This review will provide a comprehensive overview of the developments made in the field of hyperpolarized MR, including advancements in polarization techniques and delivery, probe development, pulse sequence optimization, characterization of healthy and diseased tissues, and the steps made towards clinical translation.

Contents

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1. Introduction

Molecular imaging refers to a gamut of imaging modalities that – as succinctly defined by the Radiological Society of North America (RSNA) – "directly or indirectly monitor or record the spatiotemporal distribution of molecular or cellular processes for biochemical, biologic, diagnostic, or therapeutic applications" [1]. Numerous modalities fit this description, most prominently positron emission tomography (PET) and single photon emission computed tomography (SPECT), both of which are commonly used in the clinic for diagnosing several disorders and monitoring therapeutic response [2]. More recently, fluorescent and bioluminescence optical imaging have allowed high-sensitivity molecular imaging in pre-clinical research, while computed tomography (CT) – traditionally considered a structural imaging tool – is now being used as a molecular imaging modality with the advent of cell- and tissue-specific nanoparticles and as a combined modality with PET or SPECT [3,4].

Clinical use of magnetic resonance imaging (MRI) has largely been limited to structural assessment. However, proton (^{1}H), sodium (^{23}Na), phosphorus (^{31}P), and carbon (^{13}C) MRI/ nuclear magnetic resonance (NMR) are extensively used as molecular imaging tools in pre-clinical studies in animals and cells. In these studies, the modality's foremost limitation – its low sensitivity – can be overcome by the use of longer scan times and signal averaging [5–7]. As such, molecular MRI/ NMR using conventional thermally polarized nuclei is limited to probing quasi-steady-state metabolism. The advent of hyperpolarized (HP) MRI/NMR overcomes this limitation by substantially enhancing the signal of certain biologically important probes through a process known as external nuclear polarization, enabling real-time molecular imaging with unprecedented temporal resolution. The information obtained by HP MR has significant promise in the clinic, where imaging-derived metabolomics could play a critical role in disease diagnosis and therapeutic monitoring.

Hyperpolarized MR is a burgeoning field in which investigators continue to make rapid advancements in an array of areas, which include polarization techniques and delivery, probe development, pulse sequence optimization, characterization of healthy and diseased tissues, and clinical translation. In light of the rapidly changing and multifarious nature of this technology, this review aims to provide a comprehensive overview of the current state of molecular imaging using HP MR, the developments that have led to this point, and the central challenges that hyperpolarized technology faces as it moves towards making a clinical impact.

2. Molecular imaging using non-MR modalities

Several well-established molecular imaging techniques are actively used in basic and clinical research. This section describes applications of each technology, their advantages and limitations, and how they differ from HP MRI/NMR.

2.1. PET and SPECT

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) use radioactively labeled metabolic tracers (*e.g.*, 18F-FDG,) to probe the cellular uptake of their analogous biologically relevant molecules (*e.g.*, glucose). Both techniques are widely used in clinical [2,8,9] and pre-clinical [10–13] scenarios for a broad range of applications including, but not limited to, the diagnosis, staging, and monitoring of a variety of cancers [14–18], drug development – *e.g.*, probing the bio-distribution of new pharmaceuticals [19] – and neuroimaging [20].

Although PET and SPECT provide high sensitivity for detection, they suffer from poor spatial resolution [4,21]. As a result CT or MRI are used for accurate reconstruction and anatomical localization of tracers [22]. Another major shortcoming of both modalities is that they are limited to revealing abnormalities in the uptake or retention of the tracers; they are unable to reveal changes in downstream metabolites that may be crucial to the diagnosis and staging of diseases.

On the other hand, hyperpolarized MRI – which probes analogous pathways to PET – highlights alterations in downstream metabolites using their unique ^{13}C NMR resonance frequencies, thus providing non-invasive interrogation of the size of metabolite pools and the flux through their corresponding pathways [23]. However, unlike PET and SPECT, absolute quantification of HP MR substrates can be challenging due to variations in polarization level and the use of super physiological concentrations of administered agents [24]. Furthermore, despite the large signal gains achieved using hyperpolarization, the near-unity photon detection efficiency of radionuclide agents is not achievable. Nevertheless, hyperpolarized probes can provide complementary imaging information that address the same diagnostic imaging goals as PET and SPECT.

2.2. Fluorescence and bioluminescence tomography

Optical tomography is widely used for the preclinical study of biology and pathology. The major optical techniques, fluorescence and