Editorial

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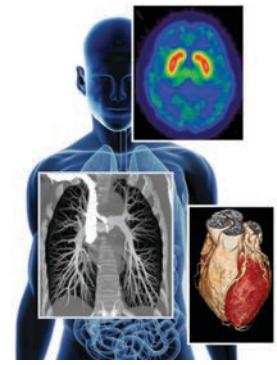

Imaging in Medicine

The benefits of not using exogenous substances to prepare substrates for hyperpolarized MRI

"...combining the use of nonionizing radiology techniques with purely endogenous contrast agents containing stable isotopes only is the most sensible approach for reducing risks of side effects to nearly zero."

Keywords: carbon 13 • dynamic nuclear polarization • hyperpolarization • metabolism • molecular imaging • MRI • nuclear magnetic resonance • photo-induced • radicals • UV

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To sustain its functions and internal processes, the human organism depends on a tightly regulated balance of chemical reactions taking place at the cellular level. These biochemical transformations, which provide energy and are the building blocks for essential biomolecules, are catalyzed by enzymes and form the pathways defining the complex network underlying cellular metabolism. Diseased cells are usually characterized by abnormal metabolic fluxes through specific pathways and an increasing number of *in vivo* and *in vitro* studies are unraveling the metabolic dysfunctions associated with various pathologies. Cancer cells exhibit particularly prevalent examples of a pathological shift in metabolism and it has been recently shown that oncogenic mutations in enzymes alter cellular metabolism [1]. Metabolic disorders have also been directly associated with cardiac failure [2,3]. Drugs targeting the key metabolic pathways are currently under investigation and may lead to the development of new therapies [4,5].

However, the imaging tools available to clinicians to detect and monitor metabolic impairments and adjustments in patients are limited. PET techniques only give information on substrate uptake and do not provide further insights into downstream metabolic processes and enzymatic reactions. In this context, the development of hyperpolarized ^{13}C MRI was undoubtedly a real breakthrough in the world of biomedical imaging since it gave an incredible boost to the sensitivity of ^{13}C MRI [6,7]. The gain in signal-to-noise ratio (SNR) of several orders of magnitude is incomparably larger than the few-fold SNR enhancement that can be achieved through the costly and technologically challenging increase in magnetic field of MRI scanners. Thanks to hyperpolarization, the *in vivo* ^{13}C signal of metabolites was up to four orders of magnitude larger, something truly exceptional. Using the fact that the carbon backbone of biomolecules can be labeled with the rare (~1.1%) stable ^{13}C isotope, the abundant (98.9%) ^{12}C isotope being undetectable by MRI, this technology allowed, for the first time, to noninvasively follow metabolism *in vivo* in real time [8]. The perspectives for imaging the metabolism of cancer cells *in vivo* was extensively discussed in a white paper commissioned by the National Cancer Institute of the US NIH [9]. The high potential of hyperpolarized ^{13}C MRI for detecting cardiac dysfunctions in patients was also recently highlighted [10,11].

Now that the first clinical trial has been successfully conducted in a cohort of patients with prostate cancer at the University of California, San Francisco (CA, USA) [12], the goal is to identify what can be improved to make this technology as attractive as possible and to fully take advantage of its potential. The instrumentation necessary to prepare hyperpolarized substrates is rather complex, but it compares favorably with the heavy infrastructure currently required to prepare the radioisotopes for PET imaging, a technique that is widely used clinically. Therefore, although some improvements can be made

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on the hardware side, including in the development of optimized ^{13}C probes for increased detection sensitivity, the main issues of the current methods for hyperpolarized ^{13}C MRI are linked to the use of persistent free radicals. These exogenous chemically unstable compounds, which can react with biomolecules, play the role of polarizing agents during the dynamic nuclear polarization (DNP) process leading to hyperpolarization. They need to be filtered out before the injection of the hyperpolarized substrates because of the potential health hazard associated with their chemical reactivity. This filtering process is an additional step that delays the injection and, since the enhanced substrate ^{13}C signal is available for a very limited amount of time, typically about a minute, any time consuming step between preparation and detection of the substrate that may be avoided will have a positive impact on the sensitivity of the MRI scan. In addition, the necessity to introduce a quality control test to insure that the residual concentration of persistent radicals is below a preset threshold value further increases the delay.

> "These exogenous chemically unstable compounds, which can react with biomolecules, play the role of polarizing agents during the dynamic nuclear polarization (DNP) process leading to hyperpolarization."

We have recently shown that the remarkable photochemical properties of the most promising endogenous substrate identified to date for clinical applications of hyperpolarized ^{13}C MRI, namely pyruvic acid, can be taken advantage of in the context of DNP [13]. By exposing frozen pyruvic acid to UV light, it is indeed possible to create a sufficiently large concentration of radicals to efficiently hyperpolarize the ^{13}C labels of the substance via dissolution DNP. These transient radicals have the advantage that they are thermally scavenged to give nonradicalar endogenous species within a fraction of a second upon dissolution. The subsequent *in vivo* SNR obtained after injection of the substrate is large enough to perform high temporal and spatial resolution ^{13}C MRI. We are convinced that this method can be extended to other molecules of biological interest, for instance, lactic acid in which a small amount of pyruvic acid or other photoexcitable molecule is incorporated. We also think that an implementation of this method for use in conjunction with the clinical polarizer developed by GE Healthcare (WI, USA) should be feasible and that the enhancement can be competitive with what can be currently obtained with the commonly used trityl radicals [14].

The two most prominent competitive advantages of using nonpersistent radicals produced by UV irradiation for dissolution DNP are the elimination of the filtration step and the absence of complex synthetic chemistry. The most appropriate and efficient persistent radicals routinely used for hyperpolarized MRI are indeed difficult to synthesize and the process is therefore costly. Hyperpolarized ^{13}C MRI can not only provide a unique metabolic contrast, but it can also be an interesting alternative for contrast-enhanced proton MRI scans such as perfusion imaging and angiographies [15]. In this case, metabolically inactive ^{13}C-labeled molecules can be used and we believe that some of them can also be hyperpolarized using photoinduced radicals to obtain purely endogenous injectable solutions. This could reduce the use of Gd-based contrast agents, which have led to toxicity issues in patients with renal insufficiency [16], and it also offers the possibility to perform certain types of imaging scans at very low field since in most *in vivo* applications the large signal of hyperpolarized ^{13}C contrast agents is essentially independent of the magnetic field strength of the MRI scanners [17]. In light of the scarcity of rare earth materials to manufacture superconducting wires used in large amount to build high-field MRI magnets and the helium shortage faced by the global market [18], low-field hyperpolarized MRI could become an attractive alternative for some types of clinical imaging scans.

In the perspective of delivering more personalized medicine, which necessitates specific diagnostic tools that can be repeatedly used to adjust treatment, it becomes increasingly necessary to ensure that the imaging technologies used to follow patients do not present a health hazard. We think that combining the use of nonionizing radiology techniques with purely endogenous contrast agents containing stable isotopes only is the most sensible approach for reducing risks of side effects to nearly zero. The use of contrast agents exempt of any trace of exogenous substances for molecular and metabolic imaging in conjunction with the versatile imaging modalities offered by MRI should thus gain more and more importance in radiology within the coming years.

Acknowledgements

A Comment would like to thank J-N Hyacinthe for his comments and suggestions.

Financial & competing interests disclosure

A Comment is supported by the Swiss National Science Foundation (grant PP00P2_133562). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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