Beyond Pyruvate: Other Polarizable Substrates

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Introduction

The availability of hyperpolarized $^{13}$C-metabolic markers has opened a new field of MR imaging. MRI as an image modality offers, in connection with a $^{13}$C-labelled hyperpolarized imaging agent, the possibility of obtaining information about molecular fate in vivo [1]. This novel platform technology offer the radiologist metabolic information of importance for medical diagnosis useful for treatment planning and follow-up. Molecular distribution patterns may be mapped by injection and imaging of one or several hyperpolarized $^{13}$C molecules simultaneously, delivering valuable information about cellular structure, permeability and metabolic state. The published research using this technology has been driven by and around the metabolic marker, $1^{-13}$C-pyruvate [2,3].

With the prototype dissolution DNP set-up [4] it is readily possible to create $^{13}$C-spin polarizations, which allow only minor further improvements on signal enhancement. More recently, the polarization build-up times have been successfully shortened by various methods to the extent where the DNP part of the methodology is highly effective [5]. Considering these successes in dissolution DNP methodology and taking the broad applicability of $^{13}$C-hyperpolarized metabolic markers into account it is timely to expand applications beyond the use of $1^{-13}$C-pyruvate as a substrate in various biomedical models.

Characteristics of $^{13}$C-hyperpolarized metabolic markers

A number of physical/chemical as well as biological challenges need to be solved in the development of new potential $^{13}$C-hyperpolarized metabolic imaging markers:

Chemical/physical challenges:

- The metabolic marker or its chemical precursor has to form a glass by itself or with a glassing agent in the solid state.
- The metabolic marker or its chemical precursor should be rapidly dissolved and have high solubility.
- The metabolic marker should have a long $T_1$ in the liquid state.

Biological challenges:

- The metabolic marker should show low toxicity at high concentrations.
- The metabolic marker should be rapidly taken up and rapidly metabolised in the relevant biological system.
To meet these challenges an experimental interdisciplinary strategy is needed, Figure 1.

Following this scheme a large number of new $^{13}$C-hyperpolarized metabolic imaging markers may be developed for evaluation in various biomedical models.

**Spectroscopic imaging strategy to identify possible $^{13}$C-hyperpolarized metabolic markers**

One of the more successful metabolic imaging markers is hyperpolarized 1,4-$^{13}$C-fumarate. This new metabolic marker allows real-time metabolic studies of the enzymatic reaction converting fumarate to malate. Several disease models have been used to investigate the mechanism of action for this new marker. Among these are oncology models [6], an ischemic model [7] and a liver injury model. In addition also a therapy monitoring study has been performed in one of the tumor models [6], Figure 2.
Hyperpolarised $1,4^{-13}C_2$-fumarate conversion to $1,4^{-13}C_2$-malate is shown to be a wide functional marker with a positive contrast in several disease models. Biochemical data from these very different models suggest two different underlying mechanisms giving rise to the observed metabolic contrast: hyperpolarised $1,4^{-13}C_2$-fumarate reports on necrosis in the models of liver injury and treated tumor, whereas it reports directly on mitochondrial dysfunction in the ischemia and oncology models.

**Expectations**

$^{13}C$-hyperpolarized metabolic marker requirements as well as strategies to meet these will be discussed. Although the demands are high on $^{13}C$-hyperpolarized metabolic markers, it will be shown that the dissolution DNP clearly has a general potential to provide valuable diagnostic information in a few minutes.

**References**

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