Smart Contrast Agents in MRI

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Zinc and copper are essential cations involved in numerous biological processes; and variations in their concentrations can cause diseases; such as neurodegenerative diseases; diabetes and cancers. Hence, the detection and quantification of these cations is of utmost importance for the early diagnosis of disease. MRI responsive contrast agents (mainly Lanthanide 3+ complexes), relying on a change in state of the MRI active part upon interaction with the cation of interest e.g. switch ON/OFF or vice versa, have been successfully utilized to detect zinc and are now being developed to detect Copper(II). These paramagnetic probes mainly exploit the relaxation-based properties (T1-based contrast agents), but also the paramagnetic induced hyperfine shift properties (paraCEST and parashift probes) of the contrast agents. The challenges encountered going from zinc to copper(II) detection are discussed. Depending on the response mechanism, the use of fast-field cycling MRI seems promising to increase the detection field while keeping a good response. In vivo applications of cation responsive MRI probes are only at their infancy and the recent developments are described, along with the associated quantification problems.

Keywords: contrast agents ; MRI ; zinc ; copper ; molecular imaging

1. Introduction

Magnetic Resonance Imaging (MRI) is characterized by a high spatial and temporal resolution, with no depth penetration limitations making it possible to image the whole body. However it suffers from low sensitivity, which can be overcome by the use of contrast agents. MRI has long been devoted to the obtention of anatomical imaging. The development of molecular imaging has led to great interest in the advancement of MRI imaging probes for specific applications. Molecular imaging seeks to visualize the expression and function of bioactive molecules, highlighting the physiological abnormalities underlying the diseases, rather than their structural consequences, which often happen at a later stage. The use of an imaging probe is essential in molecular imaging and is the component which will be selectively influenced by the biomarker being detected. Metal ions and more precisely Cu^{2+} and Zn^{2+} are particularly interesting targets as their misregulation have been linked to diseases such as cancers, neurodegenerative diseases etc.

2. Metal-Based Contrast Agents

Paramagnetic metal ions are particularly interesting as they can be used in MRI either for their relaxation properties or their paramagnetic-induced shift properties, or both. In this perspective, the chemistry of lanthanide ions is particularly exciting. They have similar chemical behaviors along the series, but possess unique physical, spectroscopic and magnetic properties. For example, Gd^{3+} due to its high electronic spin (7/2) and relatively long electronic relaxation is a choice ion for developing T_1-contrast agents. These agents affect the longitudinal relaxation time of water protons in surrounding tissues and give a positive contrast on MRI images. The lanthanide paramagnetic-induced hyperfine shifts (with the exception of Gd^{3+}) have also been used for paramagnetic chemical exchange saturation transfer (ParaCEST) or paramagnetically shifted (Parashift) probes.

However due to the toxicity of exogenous lanthanide ions, they must be used as thermodynamically stable and kinetically inert complexes.

In short, the choice of the Ln^{3+} will dictate the imaging technique to use and while similar coordinating ligands can be foreseen, small modifications on the ligands will be needed to meet the requirements of a given technique.

The vast majority of Cu^{2+} and Zn^{2+} MRI responsive contrast agents are based on paramagnetic complexes (mainly lanthanide(+III) complexes but also transition metal complexes).

3. Principle of Cation Detection

The development of MRI contrast agents for molecular imaging will require a change in the state of the contrast agent upon interaction with the biomarker of interest: switch OFF/ON or vice versa. Rather than looking for a maximum efficacy, a maximum change upon biomarker interaction will be needed to increase the sensitivity of detection. It is also easier to observe a switch ON signal rather than a switch OFF.

4. Design of T1-Based Probes

The Zn^{2+} or Cu^{2+} responsive probes are typically composed of three main parts : a paramagnetic metal-ion complexing unit (MRI active part), a M^{2+} complexing unit (specific to the cation being detected), with a linker between them.

The main difference between Zn^{2+} and Cu^{2+} contrast agents will be made on the specific binding unit, which must be selective for the desired cation vs other physiological cations, and in the case of Cu^{2+} for one oxidation state (+II) vs (+I). Due to its lower concentration *in vivo*, the selectivity is even more crucial for Cu^{2+} as a small response to Zn^{2+} will be very detrimental to achieve accurate Cu^{2+} detection. Instead of using small molecular complexes, bioinspired systems can be used to try and overcome slectivity problems.

5. Other Responsive Contrast Agents for Zn^{2+} and Cu^{2+} Detection

ParaCEST and Parashift probes have been developed mainly for Zn^{2+} detection.

6. In Vivo Detection

Only T1-based probes have been applied in vivo and most of the studies have been performed for Zn^{2+} detection.

7. Fast-Field Cycling MRI

Fast field-cycling magnetic resonance imaging (FFC-MRI) is a novel strategy in MRI that takes specific advantage of the magnetic field dependency of relaxivity, rather than on the relaxivity value at a given field. In FFC-MRI the magnetic field is changed during the imaging sequence, while in conventional MRI the main magnetic field is fixed. It is particularly powerful when the relaxivity changes are based on a change in the rotational correlation time upon binding to a protein for example.

8. Quantification Method for Cation Detection

Another important issue to solve is the quantitative detection of cations. Indeed, the early detection of diseases can be performed via the alteration of cation distribution, but in order to follow this distribution the best method would be to quantitatively assess their concentration repeatedly over time. MRI is not a quantitative technique in the sense that the signal observed depends both on the presence of the cation (or biomarker) being detected, but also on the local concentration of the agent, which is not known *in vivo*. This can be problematic as a difference of contrast can be attributed to a different concentration of cation and/or the distribution of the contrast agent. MRI has been associated with quantitative techniques (such as nuclear imaging or ^{19}F NMR) to solve this issue.
