A NOVEL GENERATION OF CONCENTRATION INDEPENDENT GD(III)-BASED MRI RESPONSIVE AGENTS

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Purpose

To demonstrate the validity of a ratiometric approach based on the measurement of the R_2/R_1 ratio, in order to design a novel generation of responsive MRI agents whose imaging response is independent of the concentration of the contrast agent.

Introduction

A responsive (elsewhere referred as smart or intelligent) MRI agent is a chemical whose contrasting properties are sensitive to a given physico-chemical variable that characterises the microenvironment in which the probe distributes. Typical parameters of primary diagnostic relevance include pH, temperature, enzymatic activity, redox potential, concentration of specific ions and low-weight metabolites. So far, several Gd(III)-based agents, whose relaxivity is dependent on the above-mentioned parameters, have been investigated.[1] In spite of the good responsiveness displayed by several of such systems, their clinical use is limited by the fact that the detected image contrast cannot be unambiguously ascribed to a change in the parameter of interest if the local concentration of the responsive agent is unknown.

So far, this problem has been tackled by an indirect determination of the local concentration of the agent by using a reference compound whose relaxivity is not dependent on the parameter of interest.[2]

In this contribution, a novel approach based on a ratiometric method, will be presented and discussed. Measuring the ratio between transverse and longitudinal paramagnetic contributions to the water protons relaxation rate, R_{2p}/R_{1p}, one attains the removal of the concentration dependence.

Results and Discussion

In order to act as ratiometric responsive probe, the R_{2p}/R_{1p} ratio of a Gd(III) agent must be dependent on the parameter of interest. Two systems have been investigated and validated *in vitro*:

- A macromolecular pH responsive system consisting of a poly-ornithine adduct in which a portion of the free amino groups of have been covalently linked to a macrocyclic Gd(III) complex. At magnetic fields higher than 1 T, the R_{2p}/R_{1p} ratio of this compound is dependent on the molecular tumbling of the metal complex covalently attached to the polymer (nanoseconds scale). Since it has been reported that the tumbling rate of cationic polyaminoacids, like poly-ornithine, is inversely dependent on the protonation degree of their basic sites, the R_{2p}/R_{1p} ratio of this macromolecular adduct will increase towards the basic side (Figure 1, right). In addition, Figure 1 (left) demonstrates that the concentration independence of the R_{2p}/R_{1p} ratio.
- A Gd(III)-loaded liposomes as potential temperature MRI reporters. In this case, the temperature dependence of the R_{2p}/R_{1p} ratio has been attained by exploiting the R_2-specific magnetic susceptibility contribution generated by the encapsulation of the paramagnetic agent in the lipidic vesiscle. Interestingly, R_{2p} is dominated by the magnetic susceptibility contribution, which decreases upon increasing temperature. Conversely, the R_{1p} values of the same system are determined by the water permeability of the liposome membrane and consequently R_{1p} increases with the temperature. As a consequence, R_{2p}/R_{1p} is temperature dependent, and, thank to the ratiometric approach, concentration independent (Figure 2).

In conclusion, the ratiometric approach may be considered a promising route for designing a novel generation of concentration-independent MRI responsive agents.

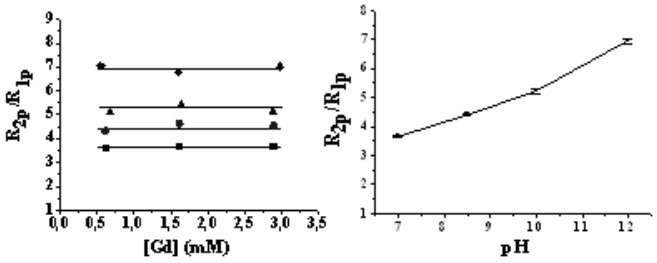

Figure 1: Left: Dependence of the R_{2p}/R_{1p} ratio on the concentration of Gd(III) for the macromolecular poly-orn-based covalent adduct at four pH values: pH 7 (squares), pH 8.5 (circles), pH 10 (triangles), and pH 12 (diamonds) (14 T, 25°C). Right: Corresponding pH dependence of the ratio calculated from the data point reported on the left.

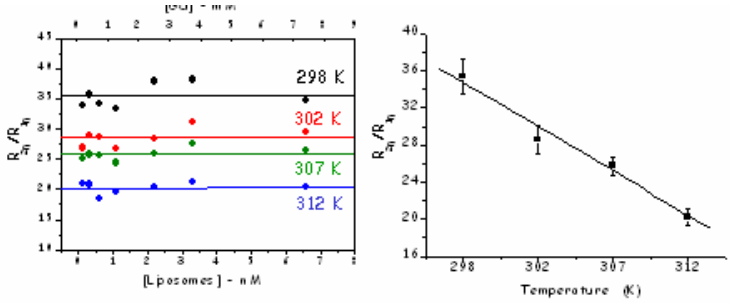

Figure 2: Left: Dependence of the R_{2p}/R_{1p} ratio (7 T) on the concentration of Gd(III)-loaded liposomes (POPC/Chol/DSPE-PEG, 55:40:5 in moles, agent encapsulated GdHPDO3A). Right: Corresponding T dependence of the ratio calculated from the data point reported on the left.

References

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