MRI of Biochemical Variables with Novel Contrast Agents

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Synopsis
Next generation MR imaging agents will report specific biochemical variables like enzyme activity, gene expression, pH, redox, tissue oxygenation, metabolite levels and other indices of metabolism. Several approaches can be taken in the design of biochemically responsive imaging agents. One can alter the T1 of bulk water using paramagnetic complexes of Gd(III), T2 using various formulations of iron oxide or other nanoparticles, or the total bulk water signal using a paramagnetic chemical exchange saturation transfer (PARACEST) agent. This lecture will review design concepts and show examples of responsive MR imaging agents that are sensitive to tissue physiology and metabolism.

Magnetic resonance (MR) is an exquisitely sensitive tool for imaging the human anatomy largely due to the abundance of water and fat protons in tissues. The tissue distribution of less abundant metabolic intermediates such as lactate, N-acetylaspartate, creatine, choline, and ATP can be also imaged by MR but only at much lower resolution. Recent widespread interest in imaging molecular events in tissues by MR has lead to renewed interest in development of imaging agents that can report biochemical variables like enzyme activity, gene expression, pH, cellular redox state, oxygenation state, and perhaps other indices of metabolism. Whenever possible one would choose to image such indices *via* the bulk water signal so that high spatial resolution images could be obtained. A typical approach might be to alter the relaxation characteristics (T_1 or T_2) of bulk water by using a paramagnetic agent that 'responds' to a biochemical event or perhaps to simply alter the total water detected in the imaging experiment. The two most widely studied paramagnetic ions in MRI to date have been iron (mostly as iron oxides) and gadolinium (presented in various chelated forms). Iron has the advantage of being a natural component of tissue and therefore considered safe even though the most widely used form is insoluble iron oxide particles. These materials make excellent line-broadening T_2 agents and examples will be given to demonstrate the potential of such materials for reporting biological events by MRI. Gd(III) is also an attractive platform for development of responsive MR imaging agents because this ion displays variable coordination chemistry with high coordination numbers and variable numbers of inner-sphere water molecules that typically exchange rapidly with bulk water molecules. The Gd(III) ion, with seven unpaired electrons, also has the highest magnetic moment of all ions in the periodic table.

Which physical parameters of a Gd(III) complex might be altered by changes in biology or physiology? The efficiency of a Gd(III) complex in relaxing bulk water protons (relaxivity) is governed by numerous physical parameters but those most often considered include changes in water coordination number (q) and changes in rotational tumbling of the complex (governed by the correlation time, τ_R). Responsive imaging agents have been designed based upon each of these parameters. Rapid water exchange is normally considered a prerequisite for an efficient Gd(III)-based contrast agent. However, the recent discovery that complexes formed between Gd(III) (or another trivalent lanthanide cation) and tetra-amide based ligands display unusually slow water exchange kinetics offers a third physical parameter that can be modulated, the bound water lifetime (τ_R). Given appropriate exchange rates and using a lanthanide ion that shifts any inner-sphere water molecules well away from bulk water, it has been shown that MR image contrast may be altered by adding a frequency selective pre-saturation pulse (at the Ln(III)-bound water position) to an imaging sequence. We have shown that the efficiency of this chemical exchange saturation transfer (CEST) effect may be optimized by rational design of the ligand and by judicious choice of the paramagnetic metal ion center. Thus, new paramagnetic complexes with slow to intermediate water exchange offer a new mechanism for creating responsive MR imaging agents that are sensitive to specific biological events and tissue physiology. Examples will be given where paramagnetic CEST agents are used to measure tissue pH, tissue glucose concentrations, and tissue redox state by MRI.