The Development of Gadolinium-Based Smart Contrast Agents for Magnetic Resonance Imaging

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Magnetic Resonance Imaging (MRI), first demonstrated in 1973,[1] has developed into an invaluable tool for medical diagnoses. MRI is a noninvasive diagnostic technique that images the ^{1}H NMR signals, primarily of water, in the body. MRI avoids the use of radioactive materials and is able to image soft tissue at any depth within the body. A drawback of MRI is poor contrast of certain diseased tissues from healthy tissues.[2]

To overcome the poor resolution, contrast agents have been developed based on paramagnetic metal centers.[2,3] The paramagnetic species acts as a relaxation agent, shortening longitudinal relaxation times (T_1) of protons on water, thereby enhancing the signal of the relaxed tissue. The paramagnetic center affects relaxation most strongly through a dipolar mechanism involving metal-bound water ligands. The relaxation enhancement is transmitted to the bulk water through exchange of coordinated water molecules. Therefore, to achieve efficient relaxation, both metal-bound water ligands and fast water-exchange with bulk solvent are needed.

The vast majority of research in the development of MRI contrast agents has utilized gadolinium ions as the paramagnetic metal center. Gadolinium, clinically used in the 3+ oxidation state, features seven unpaired electrons ($4f^7$), fast water-exchange, and a relatively long electronic relaxation time. These characteristics make Gd(III) effective at reducing T_1, thereby improving signal intensity. However, the Gd(III) free ion is toxic to biological systems. To alleviate gadolinium's toxicity, the metal ion is ligated by a multidentate chelate. Due to the ionic radius of Gd(III), coordination numbers of 8 or 9 are common. Therefore, octadentate chelates are often utilized, allowing the binding of one water ligand to the metal (Figure 1). The highly chelated metal ion is thus sequestered, greatly reducing its toxicity, but remaining in contact with the bulk solvent, enhancing the relaxation of the protons of water.

Figure 1. Examples of contrast agent coordination complexes.

First-generation contrast agents demonstrated the safety and efficacy of the multidentate complexes. Continuing work aims at improving the efficacy and target specificity of contrast agents. Increasing relaxation enhancement will lead to even

greater signal enhancement or reduce dosage sizes necessary to achieve improved image contrast.[4] Improving target specificity (i.e. controlling biodistribution) will allow for specific tissues, organs, or diseased tissues to be targeted and selectively enhanced.[5]

A new area of development involves "smart" contrast agents whose efficacy is dependent upon the local biochemical environment.[6] That is, a variable (e.g. pH) influences the contrast agent from an "off" state to an "on" state for relaxation enhancement. One group of smart contrast agents features pH-sensitive agents[6-8] that aim to detect the acidic extracellular environment of tumors as well as other acidic diseased-states of tissues. The pH controls the relaxation enhancement by modulating access of water to the gadolinium ion. A second class of smart contrast agents uses enzymatically-activated agents as substrates for a target enzyme; the enzymatic reaction modifies the agent's structure, producing an "on" state of enhancement.[6,9,10] The use of these agents allows biochemical activity to be monitored.[11] The relaxation enhancement of a third type of smart contrast agent is sensitive to the concentration of endogenous metal ions, such as Ca^{2+} (Figure 2) and Zn^{2+}.[6,2-14] These metal-sensitive agents have applications in imaging signal transduction and other cellular activities.

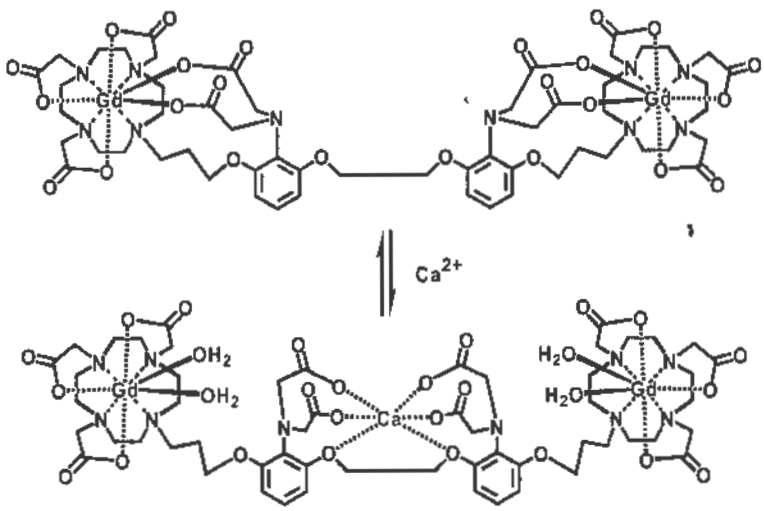

Figure 2. Example of a Ca^{2+}-sensitive contrast agent.

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