Lanthanide-based Chemical Exchange Saturation Transfer Contrast Agents in MRI

Nandini Nagraj Literature Seminar February 6th, 2007

Lanthanides or the 'rare earth' elements exhibit a wide range of magnetic, photophysical and nuclear properties that render them ideal imaging agents in many branches of diagnostic medicine.[1] Lanthanides exhibit a stable oxidation state of +3 and contain a large number of unpaired electrons. Complexes of paramagnetic lanthanide (III) ions, particularly gadolinium, have extensively been used in Magnetic Resonance Imaging as contrast agents. This is because the unpaired electrons on the Gd^{3+} are able to reduce the spin-lattice relaxation times, T_1 or increase the rate of longitudinal water proton relaxation.[2]

Chemical Exchange Saturation Transfer (CEST)[3] agents create contrast by a different mechanism in which the total bulk water signal is reduced, thereby providing a negative contrast. This is achieved by the application of a presaturation pulse at the resonance frequency of an exchanging proton site on a CEST agent. The resulting saturated or partially saturated spin is transferred to bulk water via chemical exchange. The effectiveness of a CEST agent is impacted by three factors: N, the number of exchanging protons at the presaturation frequency on the agent; τ_M, the residence lifetime of the proton on the CEST agent; $\Delta\omega$, the chemical shift difference between the two pools of protons.[4]

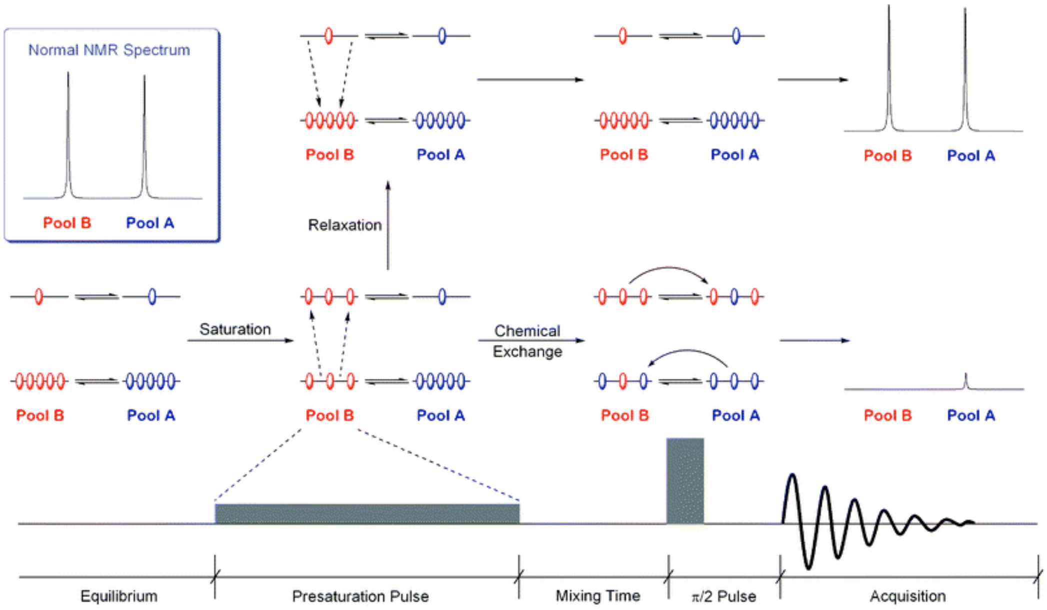

Figure 1: Schematic representation of CEST.[4]

Paramagnetic metal complexes can shift the frequency of an exchanging site in a CEST agent far away from the bulk water signal. Lanthanide ions such as Dy^{3+}, Tb^{3+}, Tm^{3+}, $Yb^{3+}$and Eu^{3+} have near ideal properties as paramagnetic CEST (PARACEST) agents.[5] Complexes formed between these lanthanide ions with neutral ligands such as tetramide derivatives of DOTA results in a decrease of the water exchange rate that has made PARACEST agents possible. The protons in close proximity to the lanthanide ion experience large hyperfine shifts, therefore, $\Delta\omega$ values are relatively large. Hence selective saturation of the protons, pool B (shown in Figure1) is possible without saturating the bulk water protons, pool A (shown in Figure 1).[4]

Recent applications include the tunable imaging of cells labeled with two different PARACEST agents shown in figure 2.[6]

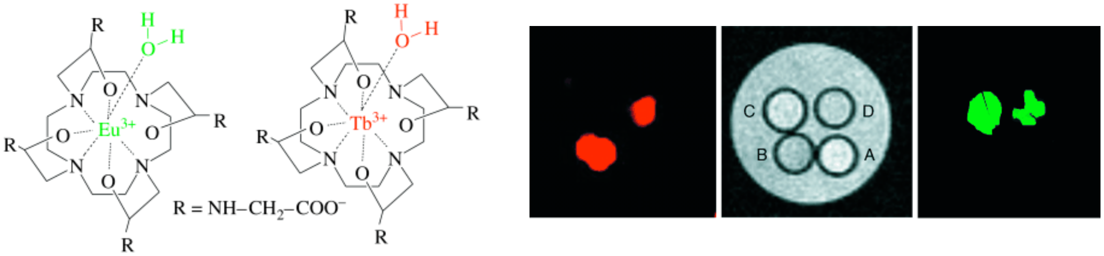

Figure 2 Structures of [Eu(dotamGly)] and [Tb(dotamGly)].MRI images of phantom with HTC cells A) Unlabeled B) Labeled with Tb^{3+} complex C) Labeled with Eu^{3+} complex D) Mixture of B and C. Right and left CEST-MRI images obtained by irradiation of metal bound protons of [Eu(dotamGly)] and [Tb(dotamGly)] respectively.[6]

Cells were incubated in the presence of both the PARACEST agents and were irradiated at 50 ppm and -600 ppm from bulk water respectively. Upon irradiation at 50 ppm downfield from the bulk water resonance, a response was detected from the Eu^{3+} complex whereas a switch to an irradiation frequency of –600 ppm from bulk water permitted detection of the Tb^{3+} complex (Shown in figure 2).[6]

Other applications include selective sensing of zinc ions,[7] detection of enzyme activity,[8] imaging of glucose,[9] MRI thermometry,[10] as well as the detection of fibrin based on PARACEST nanoparticles.[11] The use of paramagnetic lanthanide ions offers a number of advantages, including large chemical shift values from the bulk water value. This leads to increased sensitivity toward molecular imaging measurements. With the use of these PARACEST agents, one can switch the image contrast 'on' and 'off' by simply changing the pulse sequence parameters. Therefore, it is possible to minimize time delays and motion-induced artifacts inherent in normal pre-and post contrast imaging protocols developed for contrast agents based on relaxivity.[12, 13]

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