Chemical exchange saturation transfer (CEST) agents

A new class of MRI contrast agents has recently emerged that offers considerable potential for investigating biological events based on altering image contrast by a chemical exchange saturation transfer (CEST) mechanism. The first example of an exogenous CEST agent reported by Balaban and co-workers in 2000 [1] was a class of diamagnetic molecules that contain exchangeable –NH or –OH protons. In this case, MR contrast is initiated by switching on RF irradiation at the NMR frequency of an exchanging proton which then chemically exchanges into the bulk water pool thereby lowering the bulk water signal. Unlike Gd³⁺-based agents that rely upon fast water exchange between a single, highly relaxed water molecule on the Gd³⁺ complex and bulk water, this new class of CEST contrast agents requires intermediate-to-slow water exchange. Lanthane complexes having these characteristics were unknown until the recent discovery that Eu³⁺ complexes prepared from tetraamide derivatives of DOTA have unusually slow water exchange [2, 3], nearly optimal for the design of paramagnetic CEST agents. As we shall see, one advantage of using PARACEST agents to detect biological function is that chemical exchange in these systems is highly sensitive to their biological environment and this feature is relatively easily adapted to create responsive agents that have the potential of adding important physiological and biological information.

To illustrate the basics of this technique, consider two spins, A and B, in two molecules that interchange by some chemical process (Fig. 1). Examples of such chemical processes might be the γ-phosphate of ATP and the phosphate group of creatine phosphate (PCr) catalyzed by the enzyme creatine kinase, two methyl groups attached to a nitrogen atom in an asymmetrical molecule that exchange their spatial positions via nitrogen inversion or, for the purposes of the current discussion, a –NH proton on some molecule that exchanges with water protons at some rate. Again referring to Fig. 1, if the A spins are selectively saturated by use of a frequency selective RF pulse and spins A and B undergo chemical exchange during this saturation, then the intensity of the B spins will decrease to a new level. At steady-state, this new level is given by $M_{B\infty}/M_{B0} = 1/(1 + k_2 T_{1B})$, where $k_2$ is the unidirectional rate constant for spins moving from pool B to pool A (see Fig. 1) and $T_{1B}$ is the spin lattice relaxation time of the B spins. This indicates that chemical exchange saturation transfer (CEST) will be observed if the $T_1$ of bulk water (B in this model) is long compared to the lifetime $(1/k_2)$ of water at this site. Ward et al. [4] were first to suggest using CEST to alter contrast in images and demonstrated that simple diamagnetic molecules containing exchangeable –NH groups could be used to measure pH by MRI. This initial report has catalyzed a flurry of research activity on CEST agents for MRI, including endogenous exchanging groups (-NH, -OH) and exogenous CEST agents.

References
