Molecular Imaging – CEST Agents

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Chemical Exchange Saturation Transfer (CEST), distinct from Magnetization Transfer (MT), is a comparatively new method of generating image contrast by MRI. In terms of the basic acquisition parameters CEST is very similar MT: a long duration, low-power preparation pulse is applied prior to image acquisition. However, in terms of mechanism CEST is quite different in that chemical exchange is required to generate contrast. The basic requirement for CEST is a pool of protons that exchange slowly (on the NMR timescale) with the bulk water. A soft pulse applied to this pool of protons will cause saturation of the spins, subsequent exchange transfers the saturation to the bulk water, reducing signal intensity and generating contrast. Several features of this method of generating image contrast in MRI make it especially attractive to molecular imaging applications.

CEST contrast can be generated from endogenous species. The frequency of the soft saturation pulse is simply set the resonance frequency of slowly exchanging protons, such as those of amides, in that endogenous species. This approach can afford valuable information, but at best it can be no more than semi-quantitative. In general, the range of slowly exchanging proton pools in endogenous molecules is not sufficiently varied to afford the opportunity for selective saturation of one molecule. Furthermore, no calibration curve exists with which to compare the results.

CEST from exogenous species on the other hand has the potential to quantitatively define many of the prevailing parameters that molecular imaging development seeks to probe. The resonance frequency of exchangeable protons can be shifted far from those of endogenous species, facilitating selective saturation. The proton exchange kinetics can be tuned for optimal CEST, and even be made to vary in response to prevailing conditions. Furthermore, the operator is able to exercise intricate control over the CEST contrast that is generated. It can be switched on and off by the simple expedient of turning on or off the soft saturation pulse. In addition, the CEST contrast and is obtained may be varied by altering the frequency at which the soft saturation pulse is applied. In this way it is possible to conceive of molecular imaging protocols that are simply impossible with conventional T_1-shortening, or even T_2-shortening, contrast media.

The use of CEST in molecular imaging broadly breaks down into two categories: CEST in targeted imaging; and CEST in metabolic imaging. In both categories distinct advantages for CEST can be envisaged. In this contribution we will examine a range of examples of exogenous CEST contrast agents and the way in which they might be applied to molecular imaging applications.

In the context of targeted imaging we will examine the limitations of using $T_{1/2}$-shortening agents. In particular the fact that once administered contrast of these agents is always "on". The only way in which contrast can be turned "off" is for the contrast agent to eliminate from the body. This is particularly problematic in the context of iron-oxide nanoparticulate contrast agents which can take several days to clear the body. This means that all pre-contrast imaging must be completed prior to administration of the contrast material. In contrast, CEST affords the opportunity to acquire pre-contrast images even after the administration of contrast. We will explore how this feature can be exploited in targeted imaging.

In the context of metabolic imaging, conventional $T_{1/2}$-shortening agents have the problem that, once administered, they always contribute to image contrast. Furthermore, they always do so in the same way. Thus, a contrast agent designed to alter its effectiveness in response to a change in some metabolically important parameter, *i.e.* pH, will continue to affect image contrast similarly regardless the prevailing conditions. This makes it difficult, or even impossible, to differentiate between changes in the parameter of interest and changes in the concentration of the contrast agent. However, CEST contrast is not always the same, the contrast generated is dependent upon the way in which the image is collected. We will explore strategies that have been developed to facilitate metabolic imaging through the use of CEST contrast.

Finally, we will consider the challenges in hurdles that remain to be overcome in order to implement CEST contrast as a routine methodology by which molecular imaging can be accomplished.