Chemical Exchange Saturation Transfer MRI

Subjects: Pharmacology & Pharmacy

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Recently, Chemical Exchange Saturation Transfer (CEST) MRI is emerging as an attractive approach with the capability of directly using low concentration, exchangeable protons-containing agents for generating quantitative MRI contrast. The ability to utilize diamagnetic compounds has been extensively exploited to detect many clinical compounds, such as FDA approved drugs, X-ray/CT contrast agents, nutrients, supplements, and biopolymers. The ability to directly off-label use clinical compounds permits CEST MRI to be rapidly translated to clinical settings.

Chemical Exchange Saturation Transfer MRI,CEST MRI

1. Introduction

In 2000, Balaban and his colleagues demonstrated a new type of MRI contrast could be obtained by a few diamagnetic metabolites containing exchangeable protons and named it as “chemical exchange saturation transfer” (CEST) [1]. To date, CEST MRI has been exploited to detect a broad spectrum of compounds, both endogenously and exogenously. In an endogenous CEST MRI study, no contrast agent injection is required. Rather, it detects the CEST contrast stemming from endogenous molecules, which may change substantially as a result of the changes in the concentrations of biological molecules, intra- or extra- cellular pH, or cell function and metabolism, associated with pathological abnormalities. Indeed, many early CEST MRI studies have been focused on detecting the altered metabolites, protein concentration, and pH in cancer [1][2][3][4][5]. Very often, the exchangeable protons in endogenous molecules, such as proteins, are abundant, hence providing sufficient sensitivity for CEST MRI detection. As such, CEST MRI has become an appealing non-invasive technology to detect and monitor the progression of many diseases, including cancers [5][6][7][8][9], stroke [5][10][11][12][13][14][15], neurodegenerative diseases [16][17][18][19], musculoskeletal diseases [20][21][22][23], and kidney diseases [24][25][26]. Interested readers are referred to several recent reviews covering the development and applications of endogenous CEST MRI [27][28][29][30].

On the other hand, exogenous-agent-based CEST MRI can be designated to target specific molecular targets and biomarkers, thereby potentially providing higher specificity than the endogenous counterparts. By the name, the agent-based approach requires administering contrast agents, which is often referred to as a minimally invasive approach to differentiate from the imaging approaches that are completely non-invasive. Over the last two decades, hundreds of exogenous CEST MRI agents have been reported, which, based on the agent’s magnetic properties, can be categorized into diaCEST, for those use diamagnetic agents [1][29][31], paraCEST, for those use paramagnetic metal complexes [32][33][34], and hyperCEST, for those use compounds containing hyperpolarized

atoms [35][36]. Among them, diaCEST agents have the highest biocompatibility and versatility. Mounting evidence shows that diaCEST agents, including both natural compounds and synthetic agents, can be used for a broad spectrum of biomedical applications. More importantly, many clinical compounds can be directly used as diaCEST MRI agents, providing a practical way to pursue highly translatable MR molecular imaging.

2. Basics of CEST MRI

The phenomenon of intermolecular saturation transfer through proton exchange was known as early as 1960s [37]. In 1990s, in the context with development of metabolic MR spectroscopy and imaging, chemical exchange saturation transfer NMR and MRI gained a renewed interest because of the ability to detect small concentrations of molecules indirectly by the change in water MR signal [2][3][4][38][39][40], which later was named chemical exchange saturation transfer (CEST) by Ward et al. [1].

In a CEST MRI study, the magnetization of exchangeable protons are first manipulated (i.e., saturation in most of the CEST studies) using radiofrequency (RF) pulses irradiated at the specific frequency offset corresponding to the chemical shift difference between the exchangeable protons and water. For instance, the frequency offsets (Δω) are around 1.2 and 3.5 ppm (with respect to the water resonance) for hydroxyl protons on glucose and amide protons on peptide and proteins, respectively. As exchangeable protons constantly exchange between the CEST agents and water molecules, the saturated magnetization is transferred continuously from CEST agents to water, resulting in a decrease in water signal (MR image intensity). Although a single exchange-transfer process only produces a water signal decease equivalent to the number of exchangeable protons in the CEST agent pool (i.e., mM here), continuous irradiating at the frequency offsets of the exchangeable protons will pump more and more saturated protons from the CEST pool to bulky water pool (where proton concentration [H]~110 M), resulting in a substantial MR signal change, namely CEST contrast. The CEST technology thus provides a detection amplification strategy allowing detecting a small amount of exchangeable protons through a relatively large change in water MR signal. Especially for protons with relatively fast exchange rate (k_{ex} > hundreds sec^{-1}) but within the slow to intermediate regime, this strategy can provide a nearly 1000-time signal amplification [41].

The pulse sequence for CEST labeling is similar to traditional magnetization transfer contrast (MTC) labeling in that a frequency-selective RF saturation pulse (power = B_1, offset = Δω) is applied for a period of time (T_{sat}), followed by subsequent MR images acquisition. For a full spectral assessment, a range of offsets are intermittently irradiated, and one image is acquired per offset. Typically, an image without saturation pulses is also acquired as the reference image. The CEST MRI signal is often depicted using Z-spectrum, in which the normalized MR signal $(S^{\Delta\omega})/S_0$ is plotted with respect to the frequency offset of the saturation pulses (Δω), where $S^{\Delta\omega}$ is the MRI signal with RF irradiated at Δω, and S_0 is the reference signal acquired without RF saturation. The CEST contrast is commonly quantified using magnetization transfer ratio asymmetry (MTR_{asym}), defined by $MTR_{asym} = (S^{-\Delta\omega} - S^{+\Delta\omega})/S_0$, where −Δω is the frequency offsets on the opposite side with respect to the water frequency offset (set to 0). While bearing several limitations, the MTR_{asym} approach can effectively separate the CEST effect from other effects such as water direct saturation and MTC co-existing in the Z-spectrum and still is the most widely used metric in CEST MRI studies. It should be noted that the CEST contrast (MTR_{asym}) is strongly affected by

acquisition parameters such as field strength (B_0) [42][43][44], tissue intrinsic T_1/T_2 relaxation times [45][46], the shape, B_1, and length of the saturation RF pulses [45][47][48]. Importantly, it is suggested that B_1 should be adjusted with respect to the exchange rate of a CEST agent, i.e., optimal $B_1 \sim k_{ex}/2\pi$ [49]. As a result, different exchangeable protons may have different CEST-B_1 dependences. Hence, caution has to be taken when correlating the measured CEST contrast with physically meaningful parameters such as agent concentration and exchange rate. Interested readers are referred to several excellent review papers [30][33][43][48][50][51] for more details about the CEST MRI technology.

Compared to conventional MRI contrast agents, CEST MRI agents have a number of unbeatable advantages. CEST MRI has the ability to exploit non-metallic, bioorganic, biocompatible, diamagnetic compounds. As endogenous and exogenous biologically relevant molecules and compounds contain hydroxyl (–OH, 0.8–2 ppm from water), amino ($–NH_2$, 1.8–2.4 ppm), or amide (–NH, 3.5–6.3 ppm) groups, they inherently are good candidate CEST agents [27][28][51]. To date, a wide range of diamagnetic compounds (Table 1) have been investigated [52], and many of them, for example, X-ray and CT contrast agents [53][54][55], drugs [56][57][58][59], nutrients and supplements [16][41][60][61][62], and drug carriers [52][63], are clinically available agents. The advantage to use these compounds as CEST MRI agents is unprecedented: they can be used directly in humans, which is one of the most formidable challenges for the clinical use of most newly synthesized contrast agents. Besides the excellent potential of translatability, CEST MRI also has a number of technical advantages. First, unlike metallic agents that can strongly affect the inherent tissue T_1 and T_2 properties, CEST agents may be used in conjugation with other MRI methods simultaneously as exchangeable protons only slightly affect tissue T_2 times and have a negligible effect on tissue T_1 times. Moreover, CEST MRI contrast can be turned on and off at will by turning RF pulses on and off [64][65]. Hence, it is possible to simultaneously acquire other (inherent) MRI contrast and CEST MRI contrast [66][67], allowing combined detection of CEST agents with other morphologic, functional, and molecular assessments. Finally, simultaneous detection of multiple CEST agents is also possible as long as the agents have distinctive CEST offsets, which sometimes is referred to as multi-colored MRI detection [62][65][68][69].

Table 1. DIACEST library (Reprinted with permission from Ref [52]).

Exchangeable Proton	Signal Frequency Offset Δω (ppm)	Examples
Hydroxyl (–OH)	0.8–2, 4.8	Glucose [60][61][70]; 3-OMG [71][72][73] 2DG [74][75][76]; dextran [77][78]; sucralose [79]; sucrose [80]; glucosamine [81]; phenols [82]
Amide (–NH)	3.5, 4.2, 5.6	Poly-L-lysine [83]; iopamidol [84]; iopromide [55]; mobile proteins [5]
Amino ($–NH_2$)	1.8–2.4	L-arginine [62][85]; protamine [86]; cytosine/5-FC [87]; proteins [88] folate acids [59]
Heterocyclic ring	5–6.3	Barbituric acid [86]; thymidine [89]; uridin70e [90]

Exchangeable Proton	Signal Frequency Offset Δω (ppm)	Examples
amide (–NH)		
Hydrogen bonds	6–12	Salicylic acids [91]; imidazoles [92]; H_2O_2 [41]
Aliphatic protons (rNOE)	−1.6, −3.5	Mobile proteins [93][94]

Abbreviations: 3-OMG: 3-O-methyl glucose; 2DG: 2-deoxy-d-glucose; rNOE: relayed nuclear Overhauser effect.

3. Conclusions

CEST MRI is a rapidly developing technology with the unprecedented ability to directly use a broad spectrum of clinical agents and even drugs as MRI contrast agents, providing a practical way to realize “label-free” theranostics. The inventory of CEST agents keeps expanding. It is anticipated that many CEST agents may be advanced to the clinic in the near future to help diagnosis or treatment monitoring in a personalized manner.

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