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Characterization of D-Maltose as a T₂-Exchange Contrast Agent for Dynamic Contrast-Enhanced MRI

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Abstract

Purpose—We sought to investigate the potential of D-maltose, D-sorbitol, and D-mannitol as T₂ exchange magnetic resonance imaging (MRI) contrast agents. We also sought to compare the in vivo pharmacokinetics of D-maltose with D-glucose with dynamic contrast enhancement (DCE) MRI.

Methods—T₁ and T₂ relaxation time constants of the saccharides were measured using eight pH values and nine concentrations. The effect of echo spacing in a multiecho acquisition sequence used for the T₂ measurement was evaluated for all samples. Finally, performances of D-maltose and D-glucose during T₂-weighted DCE-MRI were compared in vivo.

Results—Estimated T₂ relaxivities (r₂) of D-glucose and D-maltose were highly and nonlinearly dependent on pH and echo spacing, reaching their maximum at pH=7.0 (~0.08mM⁻¹ s⁻¹). The r₂ values of D-sorbitol and D-mannitol were estimated to be ~0.02mM⁻¹ s⁻¹ and were invariant to pH and echo spacing for pH > 7.0. The change in T₂ in tumor and muscle tissues remained constant after administration of D-maltose, whereas the change in T₂ decreased in tumor and muscle after administration of D-glucose. Therefore, D-maltose has a longer time window for T₂-weighted DCE-MRI in tumors.

Conclusion—We have demonstrated that D-maltose can be used as a T₂ exchange MRI contrast agent. The larger, sustained T₂-weighted contrast from D-maltose relative to D-glucose has practical advantages for tumor diagnoses during T₂-weighted DCE-MRI.

Keywords

DCE-MRI; D-maltose; T_{2ex}; tumor imaging

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INTRODUCTION

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is often used to identify pathological tissues, such as solid tumors, by dynamically monitoring the change in image contrast after administering a contrast agent (1,2). T_1 MRI contrast agents, such as gadolinium (Gd)(III) chelates, are commonly used in DCE-MRI studies because these agents can be detected with a series of T_1 -weighted MR images that are acquired using routine acquisition protocols (3). Furthermore, Gd(III)-based contrast agents have good detection sensitivity, partly attributed to the fast 10^7 to 10^9 Hz chemical exchange rate between a water molecule bound to the agent and the surrounding bulk water. However, metallic Gd(III)-based contrast agents are potentially toxic (4), which has prompted investigations of the use of other MRI contrast agents for DCE-MRI studies.

Nonmetallic MRI contrast agents that are detected by chemical exchange saturation transfer (CEST) have been used for DCE-MRI studies (5). In particular, the hydroxyl protons of D-glucose can generate CEST contrast, and a series of CEST MR images can track the pharmacokinetics of D-glucose uptake and washout in tumor tissues (6–8). Glucose is approved for intravenous administration in patients, which has accelerated the translation of “glucoCEST MRI” for clinical DCE-MRI studies (9,10). Unfortunately, CEST MRI contrast agents have low detection sensitivity relative to relaxation-based MRI contrast agents because of the relatively slow 10 to 10^4 Hz chemical exchange rate needed to generate a CEST effect (11). This pitfall can be partly compensated by administering D-glucose to subjects at high concentrations; however, a rapid increase in blood glucose level may not be tolerable for all patients. Furthermore, CEST MRI requires the implementation of new pulse sequences that are now only recently emerging for most clinical scanners, currently limiting their broad and rapid dissemination (12).

The hydroxyl protons of D-glucose also exhibit intermediate 10^4 to 10^7 Hz chemical exchange rates that can generate MR image contrast based on the T_2 -exchange (T_{2ex}) mechanism (13,14). T_{2ex} relaxation is a result of proton exchange between an agent and water, which causes the average MR frequency (also known as the MR chemical shift) of the proton to be a time-weighted average value of the MR frequencies of the proton on the agent and water. This time-weighted average is different for each exchanging proton because proton exchange is a stochastic process. The different time-weighted average MR frequency for each proton results in a decay of net coherent magnetization, which manifests as T_2 relaxation (15). This improved sensitivity can potentially reduce the amount of glucose to be administered to a subject. The T_{2ex} relaxation mechanism can change the contrast level of T_2 -weighted MR images, which are routinely obtained in clinical radiology centers using many types of acquisition protocols. Therefore, T_2 -weighted imaging with glucose is a compelling alternative for acquiring DCE-MRI acquisitions.

As another pitfall, DCE-MRI using D-glucose can be difficult to interpret because the pharmacokinetics of this carbohydrate is confounded by its rapid metabolism in practically all tissues (16). This rapid metabolism is assumed to be responsible for only a ~10-minute change in image contrast after intravenous administration of glucose. This pitfall has led to investigations of other carbohydrates for DCE-MRI, including 3-O-methyl-D-glucose,

glucosamine, and N-acetyl-glucosamine, that are not rapidly metabolized by mammalian cells (17,18). These investigations with other carbohydrates have used CEST MRI to detect a dynamic change in image contrast.

The objective of our study was to determine whether carbohydrates other than D-glucose can be used as T_{2ex} contrast agents for DCE-MRI. Mammalian cells do not contain the cellular machinery for binding, transport, and digestion of D-maltose, D-mannitol, and D-sorbitol for energy production (19–22). Therefore, we compared the performances of D-glucose, D-maltose, D-mannitol, and D-sorbitol under multiple pH values, concentrations, and MRI acquisition conditions. Based on these initial studies, we then investigated the utility of D-maltose relative to D-glucose as T_{2ex} contrast agents for in vivo, T_2 -weighted DCE-MRI.

METHODS

Phantom preparation

Phantoms of D-maltose, D-glucose, D-sorbitol, and D-mannitol were prepared using compounds as purchased from CHEM-IMPEX International Inc. (Bensenville, IL), Sigma-Aldrich (St. Louis, MO), Santa Cruz Biotechnology Inc. (Dallas, TX), and Alfa Aesar (Ward Hill, MA), respectively. Stock solutions (100mM) at eight different pH values (5.0, 5.5, 6.0, 6.5, 7.0, 7.4, 8.0, and 8.5), as measured with a calibrated Orion Star A121 pH meter (Thermo Scientific, Waltham, MA), were prepared using distilled water and 1×phosphate-buffered saline (PBS; Hoefer Inc., Holliston, MA). Sodium azide (3% w/v; Sigma-Aldrich) for preservation was added to each sample including control samples. Stock solutions were diluted to produce seven concentrations (80, 75, 60, 40, 20, 10, and 5 mM), and 0mM 1×PBS was used as a control for each of the aforementioned pH values. A 300-μL volume of each stock was added to nine centrifuge tubes that were taped around a 50-mL tube of distilled water and positioned in a modified cradle. The phantoms were placed in a 7 Tesla (T) BioSpec MRI scanner with a 20-cm bore using a 72-mm quadrature transceiver coil (Bruker BioSpin Inc., Billerica, MA). The temperature was maintained at 37.0 ± 0.2 °C using an automated feedback system between the temperature probe and an air heater (SA Instruments, Stony Brook, NY).

T_1 and T_2 relaxation time measurements

The T_1 relaxation time of each sample was measured using a rapid acquisition with relaxation enhancement (RARE) acquisition sequence and the following parameters: repetition time (TR)=150, 300, 500, 700, 900, 1,200, 2,000, 3,000, 6,000, and 10,000 ms; echo time (TE)=9.07 ms; number of excitations (NEX)=1; RARE factor=2; slice thickness=1.0mm; field of view (FOV)=4cm²; linear encoding order; matrix=128×128; and in-plane spatial resolution=0.31mm². Total scan time was 25 minutes. The data from these experiments were fit to Equation [1] using least square curve fitting to estimate T_1 and M_0 .

$$S(TR, M_z, T_1) = M_z \cdot [1 - e^{-TR/T_1}] \quad [1]$$

The T_2 relaxation time of all samples was measured using a multispin multiecho (MSME) acquisition sequence with variable echo spacing as follows: TR=10,000 ms; NEX=1; linear encoding order; FOV=4cm²; slice thickness =1.0mm; matrix=64×64; number of slices=1; and in-plane spatial resolution=0.625mm². To ensure good signal-to-noise ratio, seven variable echo spacing experiments were performed for a total time of 600 ms, with repetitions/echo spacing of 40/15, 30/20, 24/25, 20/30, 15/40, 12/50, and 10/60 msec. The data from these experiments were fit to Equation [2] using least square curve fitting to estimate T_2 and M_0 .

$$S(TE, M_z, T_2) = M_z \cdot e^{-TE/T_2} \quad [2]$$

Finally, the T_1 and T_2 relaxivities (r_1 and r_2 , respectively) for all saccharides were measured at each pH and echo spacing fitting the data to Equation [3]:

$$\frac{1}{T_{i,k}} = r_i[CA]_k + \frac{1}{T_{i,0}} \quad [3]$$

where $T_{i,k}$ is the T_1 or T_2 relaxation time (seconds) at each concentration k , r_i is the T_1 or T_2 relaxivity (mM⁻¹ s⁻¹), $[CA]_k$ is the concentration k of the contrast agent, and $T_{i,0}$ is the T_1 or T_2 in the absence of the contrast agent.

In vivo studies

All animals were cared for in compliance with protocols approved by the Institutional Animal Care and Use Committee of the University of Arizona (Tucson, AZ). A549 human lung adenocarcinoma cells were prepared by trypsinization, rinsing once in PBS, and suspended in 50% Matrigel (BD Biosciences, Franklin Lakes, NJ) and 50% PBS. Seven male nude mice, approximately 20 g each, were injected subcutaneously in the right flank with 10×10^6 cells in 0.1mL of saline. Tumors grew to ~300mm³ before initiating MRI studies with a 7T Bruker Biospec MRI instrument and transceiver coil used for phantom studies. Before the MRI scan, each mouse was anesthetized with 1.5% to 2.5% isoflurane in O₂ carrier gas and had a 27G catheter placed in the tail vein. Physiological respiration rate and core body temperature were monitored throughout the MRI session. All animals were imaged while maintaining their temperature at 37.0±0.2 °C using warm air controlled by a temperature feedback system (SA Instruments, Inc., Stony Brook, NY).

A series of T_2 -weighted DCE-MR images were acquired using a RARE MRI protocol with the following parameters: TR=1,000 ms; echo train length=4; effective TE=30 ms; NEX=2; FOV=6.0cm²; in-plane spatial resolution =0.94mm²; matrix=64×64; and slice thickness =1.0mm, for three slices centered in the tumor. Each individual RARE image was acquired in 32 seconds and repeated 64 times. An initial set of baseline images were acquired for 2 or 10 minutes before intravenous injection of 250 μL of 3.0 mmol/kg of D-maltose solution (Sigma-Aldrich) or before intravenous injection of 250 μL of 5.0 mmol/kg of D-glucose

solution (Growcells, Inc., Irvine, CA) over 1 minute, and subsequent infusion of either contrast agent at a rate of 400 μ L/hour of either agent for the remainder of the scan, resulting in a total acquisition time of 34:10 minutes.

The change in T_2 relaxation rate $R_2(t)$ during in vivo T_2 -weighted DCE-MRI experiments was estimated as follows: First, the MRI signal was normalized to the signal before injection as described in Equation [4]:

$$\frac{S(t)}{S(0)} = \frac{(1 - e^{-TR \cdot R_1(t)}) \cdot e^{-TE \cdot R_2(t)}}{(1 - e^{-TR \cdot R_1(0)}) \cdot e^{-TE \cdot R_2(0)}} \quad [4]$$

where $S(t)$ is the MRI signal time t , $S(0)$ is the mean signal for the 2- to 10-minute baseline before injection of D-glucose or D-maltose, TR is the repetition time, $R_1(t)$ and $R_2(t)$ are the T_1 and T_2 relaxation rates at time t , whereas $R_1(0)$ and $R_2(0)$ are the T_1 and T_2 relaxation rates before injection. Next, assuming that $R_1(0)=R_1(t)$ and taking the natural logarithm on both sides Equation [4] reduces to Equation [5a], which yields in Equation [5c], where $R_2(t)=R_2(t) - R_2(0)$.

$$\ln \left[\frac{S(t)}{S(0)} \right] = \ln [e^{-TE \cdot R_2(t)}] - \ln [e^{-TE \cdot R_2(0)}] \quad [5a]$$

$$\ln \left[\frac{S(t)}{S(0)} \right] = -TE \cdot [R_2(t) - R_2(0)] \quad [5b]$$

$$\Delta R_2(t) = -TE^{-1} \cdot \ln \left[\frac{S(t)}{S(0)} \right] \quad [5c]$$

RESULTS

D-glucose and D-maltose showed a significant effect on R_2 , varying from 2 to 9 s^{-1} depending on the pH and concentration (Fig. 1; Supporting Table S1). The effect of pH and concentration was less pronounced for D-mannitol and D-sorbitol, with R_2 varying from 1.5 to 4.5 s^{-1} . None of the saccharides had a statistically significant effect on T_1 relaxation time at the concentrations and pH values used in this study (Supporting Fig. S1; Supporting Table S1).

The effects of pH and echo spacing on T_2 relaxation were evident in T_2 -weighted MR images using a spin echo acquisition sequence (Fig. 2). Although only a portion of the tube with 100-mM concentration was in the field of view, the 95% confidence intervals were excellent for determining R_1 and R_2 values from this tube, showing that the analysis of this

tube was precise. Furthermore, Figure 1 does not show systematic error at 100mM, showing that our analysis of the R_1 and R_2 of this tube was accurate. Therefore, we conducted a systematic study of the effect of echo spacing and pH on the estimated T_2 relaxivity (r_2) for D-glucose and D-maltose (Fig. 3 and Supporting Figs. S2 and S3; Table 1). Our results indicated that the T_2 relaxivities of D-maltose and D-glucose have a nonlinear relationship with pH and exhibit their highest T_2 relaxivities ($0.08\text{mM}^{-1}\text{ s}^{-1}$) at pH=7.0, whereas their r_2 values are not statistically different from zero at pH 8.0. Importantly, the measured r_2 for D-maltose is independent of echo spacing at all the studied pH values, whereas the r_2 of D-glucose is highly dependent on echo spacing, resulting in a 2-fold change in the measured r_2 at specific combinations of pH and echo spacing. For comparison, these saccharides had no effect on the T_1 of samples with concentrations used in this study.

D-glucose and D-maltose were used for in vivo studies based on their higher r_2 relaxivities measured in phantoms. We conducted a dynamic MRI study, acquiring T_2 -weighted images before and during infusion with D-maltose or D-glucose for 34:10 minutes (Fig. 4). We used an echo spacing of 30 ms based on our results with phantoms. The change in R_2 (ΔR_2) was estimated for muscle and a tumor (Fig. 4). The ΔR_2 in the muscle and tumor was significant after injection and infusion of D-glucose, almost returning to its preinjection value after 34:10 minutes. A similar change in ΔR_2 was observed after injection and infusion of D-maltose, but this change in ΔR_2 did not return to the preinjection value after 30 minutes. This sustained contrast enhancement throughout the DCE-MRI protocol was consistently observed for all 6 mice that were studied with D-maltose (Supporting Fig. S4). Although the ΔR_2 showed a difference between tumor and muscle in some mice, the ΔR_2 was similar for tumor and muscle in other mice.

DISCUSSION

Our study has shown that D-maltose is a $T_{2\text{ex}}$ contrast agent. D-sorbitol and D-mannitol also exhibit $T_{2\text{ex}}$ relaxation, but at lower r_2 relaxivity relative to D-maltose and D-glucose. We have extended the previous studies to show that the r_2 relaxivities of both D-maltose and D-glucose are highly and nonlinearly dependent on pH. D-glucose shows dependency on echo spacing near physiological pH. A possible explanation for this observation is based on the mixture of open and closed structural isomers that are under dynamic equilibrium for both D-glucose and D-maltose, thus exposing hydroxyl groups with different exchange rates at different pH values. The efficiency of the $T_{2\text{ex}}$ mechanism to create contrast is partly dependent on the echo spacing, which effectively weights the contrast based on the contribution of hydroxyl groups with different exchange rates (23). The lack of dependency on echo spacing for D-maltose shows that $T_{2\text{ex}}$ -based DCE-MRI is more robust with D-maltose than with D-glucose. D-mannitol and D-sorbitol also had no dependence on echo spacing because they have less structural degrees of freedom, thus their r_2 remains constant at pH 7.0 regardless of pH and echo spacing.

Our in vivo T_2 -weighted DCE-MRI studies showed that D-maltose and D-glucose can be detected in tumor and muscle by $T_{2\text{ex}}$ relaxation. More importantly, our in vivo results showed that D-maltose and D-glucose have different pharmacokinetic profiles in muscle and tumor tissues. We purposefully designed our in vivo studies to include an infusion of agent

to exploit the differences in metabolism of these saccharides, whereby mammalian cells metabolize D-glucose, but not D-maltose (21,22). We did not only rely on a bolus injection that was used during previous dynamic D-glucose-enhanced MRI studies, which reflect the uptake and clearance of the agent (8,14). The $R_2(t)$ attributed to D-maltose remained constant during the last 32 minutes of the experiment in both muscle and tumor tissues, but the $R_2(t)$ in muscle and tumor tissue decreased in both tissue types during the 23:30-minute infusion of D-glucose. We propose that the metabolism of D-glucose is responsible for this decrease in image contrast (24,25), whereas the lack of metabolism for D-maltose sustains the contrast.

Our results indicate that D-maltose has advantages relative to D-glucose for T_2 -weighted DCE-MRI of tumors. The sustained contrast does not require careful timing during the imaging scan session, because any image after ~10 minutes of infusion produced the same amount of contrast. T_2 -weighted DCE-MRI with D-glucose requires acquisition within the first 10 minutes after initial injection to obtain the greatest contrast. However, dynamic MRI with D-maltose has limitations. D-maltose is not yet approved for clinical use. Similar to D-glucose, D-maltose has a r_2 relaxivity that is 10-fold lower than the r_2 of Gd- and Fe-based agents requiring administration of large quantities of D-maltose (and D-glucose) to achieve detectable changes in T_2 (26,27). The biocompatibility of D-maltose at high concentrations needed for detection will be required to provide a translational pathway to the clinic for this technique.

Our results may be used to support future studies that use spin-lock acquisition methods to detect carbohydrates during DCE-MRI studies (28). A direct comparison of spin-lock and CEST MRI techniques showed that a version of spin-lock MRI applied on water resonance provides more sensitivity for detecting carbohydrates with intermediate chemical exchange rates (29). In general, “on-resonance” acquisition methods that manipulate water resonance to generate contrast based on chemical exchange lack specificity for detecting a single metabolite, relative to “off-resonance” acquisition methods that directly manipulate the resonance of the metabolite. However, the on-resonance spin-lock MRI acquisition method avoids this problem by monitoring the change in contrast before and after the contrast agent is administered to the subject, which can be assigned to the agent with good specificity. Based on the merits of this approach, spin-lock DCE-MRI methods have recently been tested with patients who have glioblastoma (30,31). Spin-lock MRI methods have been used to detect other carbohydrates, including 2-deoxyglucose and 3-Omethyl-glucose, that showed DCE MR image contrast that lasted longer than contrast generated with glucose (32–34). Therefore, our sustained T_2 -weighted contrast during DCE-MRI results with D-maltose indicate that D-maltose may also be useful for spin-lock DCE-MRI studies.

CONCLUSIONS

Our report confirms previous studies that indicate D-glucose is a suitable T_2 -weighted DCE-MRI contrast agent. We have also extended these previous studies to characterize D-glucose, D-maltose, D-sorbitol, and D-mannitol with respect to pH and echo spacing. We identified D-maltose as an alternative T_2 -weighted DCE-MRI agent to D-glucose, which showed sustained uptake and higher contrast in tumor relative to muscle.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIG. 1.

T_2 relaxation (s^{-1}) of: (a): D-maltose; (b): D-glucose; (c): D-sorbitol; and (d): D-mannitol as a function of concentration (mM) and pH at 7.0 T and 37 °C. 95% confidence intervals for T_2 relaxation at each concentration is shown, with some confidence intervals that are smaller than the data symbol. R^2 values are 0.99 for all curves fitted with linear regression.

FIG. 2. Representative T₂-weighted MRI using D-maltose as a contrast agent. D-maltose solutions were prepared at multiple pH values and concentrations, and imaged with a RARE acquisition sequence with echo spacing (ES) of 60 ms (top row) or 120 ms (bottom row) at 7.0 T and 37 °C. The MR signal was normalized to the voxel with the maximum intensity in all six panels.

FIG. 3. T₁ relaxivity (r₁) and T₂ relaxivity (r₂) as a function of pH and echo spacing (ES) of 20, 40, or 60 ms for (a): D-maltose; (b): D-glucose; (c): D-sorbitol; and (d): D-mannitol at 7.0 T and 37 °C. 95% confidence intervals are shown for r₁ and r₂ at each measured pH.

FIG. 4. In vivo DCE-MRI using saccharides as T_{2ex} contrast agents. T_2 -weighted anatomical images before infusion of (a): D-maltose and (c): D-glucose show the regions of the tumor and muscle that were analyzed. The time-dependent changes in $1/T_2$ for the tumor and muscle regions for (b): D-maltose infusion and (d): D-glucose infusion show that these saccharides have different pharmacokinetics. The window for infusion of either maltose or glucose is denoted by the start of infusion (green asterisk) and end of infusion (red asterisk).

Table 1

Effect of pH on T_1 (r_1) and T_2 (r_2) Relaxivities of Saccharides at TE=15 ms

Maltose				
pH	r_2 ($\text{mM}^{-1} \text{s}^{-1}$)	95% CI ^a	r_1 ($\text{mM}^{-1} \text{s}^{-1}$)	95% CI ^a
5.0	0.060	0.011	0	0.006
5.5	0.018	0.004	0.001	0.008
6.0	0.048	0.002	-0.003	0.003
6.5	0.049	0.002	-0.003	0.006
7.0	0.075	0.003	-0.002	0.004
7.4	0.064	0.007	-0.005	0.004
8.0	0.01	0.002	-0.002	0.002
8.5	0	0.006	-0.003	0.009
Glucose				
pH	r_2 ($\text{mM}^{-1} \text{s}^{-1}$)	95% CI ^a	r_1 ($\text{mM}^{-1} \text{s}^{-1}$)	95% CI ^a
5.0	0.042	0.008	0.006	0.005
5.5	0.045	0.011	-0.001	0.004
6.0	0.033	0.005	-0.002	0.005
6.5	0.056	0.003	0.007	0.004
7.0	0.050	0.002	0.002	0.009
7.4	0.032	0.007	0.001	0.004
8.0	0.012	0.003	0.003	0.008
8.5	0.003	0.002	0.001	0.002
Sorbitol				
pH	r_2 ($\text{mM}^{-1} \text{s}^{-1}$)	95% CI ^a	r_1 ($\text{mM}^{-1} \text{s}^{-1}$)	95% CI ^a
5.0	0.020	0.005	0.002	0.003
5.5	0.022	0.006	0.005	0.002
6.0	0.026	0.003	0.004	0.004
6.5	0.027	0.024	0.004	0.006
7.0	0.024	0.001	0.002	0.005
7.4	0.012	0.001	-0.001	0.004
8.0	0.004	0.001	0.006	0.009
8.5	0.002	0.004	0.005	0.005
Mannitol				
pH	r_2 ($\text{mM}^{-1} \text{s}^{-1}$)	95% CI ^a	r_1 ($\text{mM}^{-1} \text{s}^{-1}$)	95% CI ^a
5.0	0.014	0.006	0.002	0.008
5.5	0.022	0.007	0.002	0.005

Maltose				
pH	r_2 (mM ⁻¹ s ⁻¹)	95% CI ^a	r_1 (mM ⁻¹ s ⁻¹)	95% CI ^a
6.0	0.024	0.002	-0.005	0.005
6.5	0.024	0.002	0.001	0.005
7.0	0.024	0.001	-0.001	0.003
7.4	0.011	0.002	-0.003	0.003
8.0	0.005	0.001	0.006	0.006
8.5	0.001	0.002	-0.005	0.004

^a95% confidence intervals shown for data at each corresponding pH value.