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Chemical exchange-sensitive spin-lock (CESL) MRI of glucose and analogs in brain tumors

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Abstract

Purpose—Glucose uptake and metabolism can be measured by chemical exchange sensitive spin-lock (CESL) MRI with an administration of glucose or glucose analogs. This study investigates the sensitivity, the spatiotemporal characteristics, and the signal source of glucoCESL with a 9L rat brain tumor model.

Methods—Dynamic CESL MRI with intravenous injection of D-glucose (Glc), 2-deoxy-D-glucose (2DG) and L-glucose were measured and compared with Gadolinium-based dynamic contrast-enhanced (DCE) MRI.

Results—The CESL signals with an injection of glucose or analogs have faster and larger changes in tumors than normal brain tissue. In tumors, the CESL signal with 2DG injection has larger and slower peak response than that with Glc due to the accumulation of 2DG and 2DG-6-phosphate in the intracellular compartment, while L-glucose, which cannot be transported intracellularly by glucose transporters, only induces a small change. The initial glucoCESL maps (<4 min) are qualitatively similar to DCE maps, whereas later maps (>4 min) show more widespread responses. The rise times of Glc-CESL and 2DG-CESL signals in the tumor are slower than that of DCE. Our data suggest that the initial CESL contrast mainly reflects a passive increase of glucose content in the extracellular space of tumors due to a higher vascular permeability, while the later period may have a significant contribution from the uptake/metabolism of glucose in the intracellular compartment.

Conclusions—Our results demonstrate that glucoCESL MRI has both extracellular and intracellular contributions, and can be a useful tool for measurements of both vascular permeability and glucose uptake in tumors.

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Keywords

Brain tumor; CEST; CESL; glucose and analogs; uptake and metabolism; vascular permeability

Introduction

Most solid tumors are characterized by both a high glycolysis rate and increased vascular permeability (1,2). Tumor vascular permeability is often assessed by dynamic contrast-enhanced (DCE) MRI with gadolinium-based contrast agents, but there is an increasing safety concern of gadolinium exposure in recent years (3–8). Glucose metabolism is commonly measured by positron emission tomography (PET) with fluorine-18-labeled 2-deoxy-D-glucose (FDG). However, the inherent ionizing radiation exposure and high cost can limit the scan frequency and exclude certain patient groups (9–14). Compared with the imaging of glucose metabolism or vascular permeability alone, the combination of both metabolism and permeability metrics can provide a better understanding of tumor biology and improve the accuracy of the diagnosis and assessment of the therapy response (15–17). Thus, an MRI technique that can simultaneously probe both glucose metabolism and vascular permeability with a safer contrast agent would improve cancer diagnosis and patient care.

Recent studies have shown that non-radio-labeled D-glucose (Glc) or its analogs can be detected indirectly by MRI through a change of water signal via chemical exchange saturation transfer (CEST) (18–21). This glucoCEST approach has been applied for the detection of tumors in animals (19,20), as well as patients (22). However, the sources of the CEST contrast with Glc administration are complex and not fully understood. It is controversial whether the CEST signal in tumors mainly measures the metabolism component, i.e. hyperglycolysis (20), or is mainly due to the glucose transport and blood flow, i.e. a higher vascular permeability (19). There are also technical challenges for glucoCEST because CEST is optimal for slow chemical exchange on the NMR time scale (23,24), whereas the glucose hydroxyl-water proton exchange is very rapid ($\sim 4500 \text{ s}^{-1}$) under physiological conditions (25,26).

A chemical exchange-sensitive spin-lock (CESL) technique has been suggested as an alternative to improve the sensitivity over CEST for intermediate to fast chemical exchange (25,27). During spin-locking period, the decay of the water signal is determined by $T_{1\rho}$, the spin-lattice relaxation time in the rotating frame. Addition of Glc or its analogs increases the relaxation rate $R_{1\rho}$ ($= 1/T_{1\rho}$) due to hydroxyl-water exchange-mediated relaxation. Pilot studies have also shown the feasibility of CESL to detect brain tumors in rodents with 2DG injection (28) as well as in glioblastoma patients following injection of Glc (29,30). Still, the discrete contributions to the glucoCESL signal have not been determined.

In this work, we studied the sensitivity and spatiotemporal characteristics of the glucoCESL signal for the detection of 9L brain tumors in rats. Two different Glc doses were injected to evaluate the dose-dependent sensitivity. CESL MRI with an injection of Glc, 2DG, and L-glucose (L-Glc) were compared to elucidate the signal source. Additionally, DCE MRI was

acquired to assess blood-brain barrier (BBB) permeability and to estimate what aspect of the glucoCESL signal is due to extravasation of glucose into tissue.

Methods

Tumor model

All animal studies were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pittsburgh. Adult male Fisher 344 rats (Charles River, Wilmington, MA) weighing between 200 and 250g were anesthetized with ~2% isoflurane. A burr hole was drilled into the right hemisphere at stereotaxic coordinates of 0 to 0.5 mm from bregma, and 3 to 3.5 mm from the midline. Inoculation of 100,000 – 300,000 9L cells (ATCC® CRL-2200™) in a total volume of 5 μ L was performed at 4 mm below the surface of the dura. After the induction of tumor cells, rats were imaged after 3 to 5 weeks when the tumor reached appropriate volume. After MRI studies, animals were perfused transcardially with PBS and then with 4% Paraformaldehyde, and the brains flash frozen and stored at -80°C . Hematoxylin & Eosin (H&E) staining was performed by the Histology Lab Core of the McGowan Institute for Regenerative Medicine. The $2\times$ magnification image shown in Figure 1C was acquired from each hemisphere individually over neighboring fields of view in the same brain section and a composite image over the full brain section was made with global intensity normalization in ImageJ (NIH).

Animal Preparation

Tumor-bearing animals weighing between 234 and 281 g ($n = 12$) were anesthetized with isoflurane (5% for induction and 2% during surgery) in a mixture of O_2 and air gases. The O_2 concentration was kept at ~30% throughout the experiment. The right femoral vein was catheterized for the delivery of maintenance fluid and injection of contrast agents, and the femoral artery was catheterized to monitor the arterial blood pressure. After surgery, the isoflurane level was reduced to ~1.5 % during MRI scans. The dynamic blood pressure and end-tidal CO_2 were monitored. The end-tidal CO_2 level was kept within 3.0 – 4.0% and the rectal temperature was maintained at $37.5 \pm 1.0^{\circ}\text{C}$ using a feedback-controlled heating pad. Glucose and analogs were dissolved in distilled water to 30% w/v concentration. For DCE-MRI, 0.15 ml of Gd-DTPA was injected. Following the injection of contrast agents, 0.5 ml of saline was injected immediately to flush the venous line. The duration is about 0.5 min to 1-min for all injections.

MR experiments

All experiments were performed on a 9.4 T magnet with a detunable volume excitation and surface receiver coil combination (Nova Medical Inc, Massachusetts, USA). To ensure stable animal physiology during the experiments, CESL experiments were performed after a 30 to 60 minute stabilization period inside the magnet. Before the CESL experiments, a T_1 map was first acquired to determine the tumor region, and a B_1 -map was acquired to determine the transmitter power (31).

In a CESL time series, images without and with $T_1\rho$ -weighting (i.e., TSL = 0 and 50 ms) were acquired in an interleaved manner. For images with a spin-lock preparation, 50-ms

spin-lock irradiation at $\gamma B_1 = \sim 500$ Hz was sandwiched between an adiabatic half-passage pulse and an inverse adiabatic half-passage pulse (each of 1.5-ms duration) (25,32). For the TSL = 0 images, the spin-lock preparation was turned off. Immediately after the spin-lock preparation, MR images were acquired using a two-segment spin-echo EPI with a field of view $2.56 \text{ cm} \times 2.56 \text{ cm}$ and one or two slices of 1.5-mm thickness. The repetition time was 2.5 s for each segment (5 s per image), and the echo time was 8.5 ms. The matrix size was 96×96 for all experiments, except the 0.5 g/kg Glc injection data where the matrix size was 64×64 . In each repetition unit, one TSL = 0 image and two TSL = 50 ms were acquired, therefore, the temporal resolution of CESL study was 15 s.

Four experiments were performed:

- 1) 0.5 g/kg of Glc (n = 5) or 1 g/kg Glc (n = 4) was injected to study the dose-dependent sensitivity and the spatiotemporal characteristics of Glc-CESL.
- 2) 0.25 g/kg of 2DG (n = 6) was injected to detect the glucose metabolism-weighted contrast of brain tumor. Our recent studies in healthy rat brain suggest that the CESL signal after such a 2DG injection is mainly sensitive to glucose metabolism (33), especially at later time periods (e.g., >20 min post-injection).
- 3) 0.25 g/kg of L-glucose (L-Glc, n = 4) was injected to gain a better understanding of the source of the CESL signal in the tumor. L-Glc is an enantiomer of Glc and has the same chemical exchange properties, however, L-Glc can only enter the extracellular space due to the leakage of BBB because it cannot be transported by glucose transporters.
- 4) After all the CESL studies, T_1 -weighted EPI images (n = 4) were acquired for a total duration of 13 min, i.e., 3 min before to 10 min after an injection of Gd-DTPA to delineate the tumor region. The repetition time was 1 s for each image (0.5 s/segment).

The injections to each individual animal were listed in Table 1. Five of the twelve animals received only one dose of Glc or Glc-analog, while the remaining seven received one Glc dose and one dose of either 2DG or L-Glc. In animals receiving two doses, CESL data with Glc injection were first acquired, and 2DG or L-Glc was injected more than 2-hr after the Glc injection so that the blood glucose level returned to baseline (18,25). For Glc- and 2DG-CESL, the images were acquired for a total of 60 minutes, i.e., 15 min before and 45 min after an intravenous injection. For L-Glc-CESL, the acquisition was for a total of 40-min, 15-min before and 25 min after the injection.

Data analysis

Data were analyzed with in-house Matlab® programs and STIMULATE software (34). Images of each CESL run were first rearranged to obtain time series of images with TSL = 0 and TSL = 50 ms. Then, a time series of $R_{1\rho}$ was calculated by pixel-wise fitting to $R_{1\rho} = \ln(S_{\text{TSL}=0}/S_{\text{TSL}=50 \text{ ms}})/50 \text{ ms}$. To determine a change of $R_{1\rho}$, Student's *t*-tests were performed on a pixel-by-pixel basis to compare the pre- and post-injection data. Baseline data were from the period spanning 15 minutes before the start of injection. The data for 2DG- and L-Glc injection induced changes were calculated from periods spanning 1-45

minutes and 1-25 min post-injection, respectively. To examine the time-dependence of the Glc-CESL contrast, two post-injection periods of 1-4 min and 4-20 min were analyzed. The

$R_{1\rho}$ maps were obtained where a threshold of $p < 0.05$ and a minimum cluster size of 4 pixels were applied except for the low-resolution study (0.5 g/kg Glc injection) in which 3 pixels were applied.

Quantitative ROI analyses were performed for the tumor and the contralateral tissues, as determined from T_1 maps. $R_{1\rho}$ time courses from all pixels within ROIs are presented as averages over 0.5-minute intervals and are shown as the mean $\pm$ standard deviation. To compare the temporal characteristics of CESL and DCE signals, the rising period of each CESL $R_{1\rho}$ time course was fitted to a Sigmoid function and the rise time from 10% to 90% of the peak was measured.

Results

Fig. 1A shows the MRI and the H&E staining images of a representative rat brain. The glioma can be identified as a hyperintense region in the T_1 map and a hypointense region in the baseline $R_{1\rho}$ map, both due to an increased water content. The presence of glioma is confirmed by the higher cellularity from the H&E staining of histological brain sections, where the images of Figs. 1C, 1D, and 1E were obtained from pink, green and blue boxes in Fig. 1B, respectively.

With a 0.25 g/kg 2DG injection (Fig. 2A), the $R_{1\rho}$ map shows a widespread signal increase in normal tissue and an even higher increase in the tumor (more yellow pixels). Fig. 2C shows the averaged time courses of the $R_{1\rho}$ change obtained from an ROI of contralateral tissue versus that from the tumor. In the tumor, $R_{1\rho}$ rises rapidly for the first 2 min or so, but the increase becomes slower after this initial period. It reaches a peak of 0.55 s^{-1} at ~ 25 min and sustains for the rest of the time course. In the contralateral tissue, $R_{1\rho}$ increases more gradually, reaching a plateau after ~ 25 min. With 0.25 g/kg L-Glc injection (Fig. 2B), there is little change in the normal tissue and a small increase of $R_{1\rho}$ in the tumor. The $R_{1\rho}$ of tumor rises quickly to 0.11 s^{-1} at ~ 2 min post injection and then remains relatively constant (Fig. 2D). Assuming that the extracellular 2DG contribution in the tumor can be estimated by the L-Glc-CESL signal, the subtraction of L-Glc data from the 2DG data would roughly indicate the CESL signal from intracellular 2DG and 2DG-6-phosphate. This is illustrated by the blue curve in Fig. 2E which shows a gradual increase up to 25 min.

With 1 g/kg Glc injection, the $R_{1\rho}$ maps averaged from 1-4 min and 4-20 min post-injection show a clear difference (Fig. 3A and 3B). An increase of $R_{1\rho}$ can be seen in the tumor in both maps. In the contralateral hemisphere, the increase of $R_{1\rho}$, which is smaller than that of the tumor, can only be seen in the later period. Qualitatively, the 1-4 min $R_{1\rho}$ map appears similar to the DCE map (Fig. 3C), whereas the 4-20 min $R_{1\rho}$ map appears similar to the 2DG-CESL map (Fig. 3D). In Fig. 3E, the tumor shows a faster and larger increase of $R_{1\rho}$. After reaching a peak at ~ 8 to 10-min, the $R_{1\rho}$ in the tumor decreases faster than of normal tissue and returns to baseline at ~ 40 min in both regions. For a lower spatial-resolution, tumors can be detected with a lower Glc dose of 0.5 g/kg (Fig. 4). The time-dependent $R_{1\rho}$ maps and the time courses of $R_{1\rho}$ are similar to those of 1 g/kg. The

peak magnitude of $R_{1\rho}$ is about 0.25 s^{-1} for the 0.5 g/kg dose compared to 0.53 s^{-1} for the 1 g/kg dose, indicating a linear dose-dependence.

The kinetics of glucoCESL signal with different Glc-analogs can shed light on their signal source. Fig. 5 compares the rising period of the $R_{1\rho}$ time course of Glc, 2DG and L-Glc injections with that of DCE-MRI. With DCE MRI (Fig. 5A), the signal increases rapidly in the tumor, reaching a peak at ~4 min. The rising periods of the $R_{1\rho}$ time courses were fitted to Sigmoid functions and interpolated to 0.05 s (Fig. 5B). In Figs. 5C and 5D, the normalized time courses and the 10% to 90% rise time were compared for Gd, L-Glc, Glc, and 2DG injections, respectively. Both figures show that the rise time of Glc-CESL is faster than that of 2DG but is slower than that of DCE.

Discussion

Source of glucoCESL signal in brain tumors

Our results show that the $R_{1\rho}$ change is always larger in the tumor than normal tissue for CESL MRI with an injection of Glc, 2DG or L-Glc, but the $R_{1\rho}$ time courses for these three injections show different spatiotemporal characteristics, indicating their different transport and metabolic properties. The change of $R_{1\rho}$ in 2DG-CESL can mainly be attributed to the fact that the metabolic product of 2DG (2DG-6-phosphate) is trapped in brain cells and accumulates during the time of CESL experiments. The injection of L-Glc yields much smaller $R_{1\rho}$ change than 2DG for the same 0.25 g/kg dose, suggesting that in the 2DG-CESL signal the contribution from the BBB leakage should be small, and the contrast between tumor and normal tissue is mainly caused by an elevated glucose uptake and metabolism in the intracellular compartment.

The rise time of Glc-CESL is faster than 2DG-CESL but is slower than that of DCE-MRI. Note that an increase in the DCE MRI signal indicates an extracellular accumulation of Gd-DPTA molecules in brain tumor due to the leaky vasculature. If the Glc-CESL signal arises solely from the extracellular-extravascular space, its rise time should not be much slower than DCE-MRI, because Glc can enter the extravascular space via passive leakage as well as active glucose transport across the BBB. The slower time-to-peak of Glc-CESL signal suggests that it also has contributions from the uptake of glucose in the intracellular space. Note that the $R_{1\rho}$ map from 1-4 min post-injection is similar to that of the DCE-MRI map, whereas the $R_{1\rho}$ map from 4-20 min post-injection is similar to that of a $R_{1\rho}$ map of 2DG-CESL. These results suggest that the $R_{1\rho}$ contrast from the initial period is mainly caused by the increased vascular permeability, whereas the $R_{1\rho}$ contrast from the later period has a large contribution from the elevated glucose uptake/metabolism.

Because intravascular signal has minimal contribution to the CESL signal response (25,33,35), the increase of $R_{1\rho}$ indicates an increase of Glc and hydroxyl-containing metabolic products in the extravascular space. Note the increase of intravascular blood glucose concentration after 1 g/kg bolus injection is ~17 mM and 9 mM at 2 min and 10 min post-injection, respectively (18,25). Assuming each mM of Glc contributes to an $R_{1\rho}$ of 0.067 s^{-1} (25), a tumor extracellular volume fraction of ~30%, and the Glc concentrations of intravascular space and the extravascular-extracellular space quickly equilibrate due to the

BBB leakage, the injection-induced increase of Glc concentration in the extravascular-extracellular space would contribute 0.34 s^{-1} ($=17\text{mM} \times 30\% \times 0.067\text{s}^{-1}/\text{mM}$) and 0.18 s^{-1} to the total $R_{1\rho}$ at 2 min and 10 min, respectively. Because the measured $R_{1\rho}$ with 1 g/kg Glc injection (Fig. 3E) is 0.34 ± 0.12 at 2 min post injection and reach a peak of 0.53 ± 0.13 at ~ 10 min post-injection, we can calculate that the glucoCESL signal contribution from the extracellular space is almost 100% at 2 min and is only $\sim 34\%$ at 10 min post-injection. This rough estimation supports that the initial Glc-CESL signal response (1-4 min) mostly originates from the BBB-leakage, whereas the later period (4-20 min) has a large contribution from the uptake of glucose to tumor cells. Compare to the normal tissue, Glc-CESL signal reaches peak faster, likely due to the extravasation via the leaky BBB and a faster uptake to the intracellular space. After reaching the peak, the Glc-CESL signal drops and returns to baseline faster, which may be attributed to a faster glucose metabolism in the tumor.

The glucoCESL-based method has been applied for the detection of glioblastoma in patients at 7 T (29,30,36). Compared to this study which acquired a time series of images with different TSL values for the calculation of $R_{1\rho}$, these human studies only acquire a time series of $T_{1\rho}$ -weighted images, which can increase the temporal resolution and possibly the sensitivity to detect the tumor. In one of these studies, the tumor region detected by CESL is different with that of DCE-MRI (30), suggesting that glucoCESL has different sources than DCE-MRI and may not arise from a leaky BBB only. The temporal behavior is similar for the tumor and the normal tissue, which is different with our Glc-CESL results. This discrepancy might be due to a higher heterogeneity of human brain tumors and the slow injection rate used by Scheuenke et al.

CESL versus CEST for the detection of glucose

Recently, CEST with Glc injection has been applied to study tumors (19,20,22). A variant of CEST, dubbed dynamic glucose-enhanced (DGE) imaging, was also proposed to detect brain tumors (37,38). Both DGE and CEST signals in normal brain tissue increase rapidly and return to the pre-injection baseline within 3-10 minutes of a Glc injection (18,38), suggesting that these signals may have a large vascular contribution. Compared to glucoCEST which acquires label and reference images with saturation frequencies at 1.2 and -1.2 ppm, respectively, the DGE approach only acquires one saturation-prepared image at the hydroxyl frequency of 1.2 ppm. While this approach increases the temporal resolution, it may have more contamination from non-chemical exchange effects. For example, a recent study suggested that the DGE signal may have significant contamination from an osmolality effect (39). Note that injection-induced elevation of osmolality also affects the CESL signal, as reported in recent studies of CESL with multiple spin-lock powers or with an “osmolality control” experiment (25,33,35,40). The magnitude of this effect is related to the concentration gradient between intravascular and extravascular glucose (or analogs). While this effect cannot be determined from our data measured with only one spin-lock power, we expect that in the tumor the relative contribution from the osmolality effect should be much smaller than normal tissue because glucose molecules can enter the extravascular-extracellular space (so that the glucose concentration equilibrates) much faster via the leaky BBB.

Another possible discrepancy between CESL and CEST is related to a pH-gradient between the intracellular and extracellular microenvironments (41,42). Cancer cells produce energy mostly by a high rate of glycolysis followed by lactic acid fermentation in the cytosol, i.e. the “Warburg effect”, leading to an acidic pH in the extracellular microenvironment, while the intracellular space is able to maintain a neutral pH. Note that CEST is more sensitive to slow chemical exchange, whereas CESL is more sensitive to chemical exchange in the intermediate regime time scale (27,43). Therefore, in glucoCEST, the Glc in the acidic extracellular space may have much larger weightings than the Glc (or hydroxyl-containing glucose metabolites) in the intracellular space (19). In contrast, our phantom study showed that CESL $R_{1\rho}$, with a selection of 500 Hz for the spin-lock frequency, is only weakly affected by the pH range of 6.8 to 7.4 (25). Therefore, glucose in the intracellular and extracellular space would have similar weighting to the CESL signal.

Conclusion

We found that brain tumors can be detected by CESL MRI with an injection of glucose and 2DG. While 2DG-CESL likely indicates the contrast in glucose uptake/metabolism, CESL with Glc injection is sensitive to BBB leakage and glucose uptake in the initial and later period, respectively. Our results suggest that glucoCESL has sufficient sensitivity and can be applied to the diagnosis and prognosis of brain tumors, offering a safe alternative to the conventional FDG-PET and DCE-MRI methods.

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Fig. 1.

Comparison of MRI and H&E staining images of a representative rat brain with glioma. Glioma can be detected by T₁ map (A), and baseline R_{1ρ} map (B). H&E staining images were obtained with 2× magnification from the pink box (C), and 10× magnification from the green (D) and blue (E) boxes of (B). The solid and dashed cyan contours in (A) delineate the tumor and contralateral normal tissue ROIs used for quantitative analysis, respectively.

Fig. 2.

Comparison of CESL data from an injection of 0.25 g/kg of 2DG and L-Glc. The $R_{1\rho}$ maps from 2DG (A) and L-Glc (B) shows different sensitivity. The time courses of $R_{1\rho}$ from 2DG (C) and L-Glc injections (D) show larger $R_{1\rho}$ for 2DG and larger $R_{1\rho}$ in the tumor region. The intracellular CESL signal in the tumor (E) can be roughly estimated from the difference between 2DG and L-Glc data. The gray bars indicate the injection period.

Fig. 3.

GlucoCESL data with 1 g/kg Glc injections. The $R_{1\rho}$ map averaged from 1 to 4 min after the injection shows an increase of $R_{1\rho}$ mostly within the tumor region (A), which is qualitatively similar to the DCE MRI map (C). In contrast, the $R_{1\rho}$ map averaged from 4 to 20 min after injection shows a larger increase in the tumor and a smaller increase in contralateral normal tissue (B), which is similar to the $R_{1\rho}$ map with 0.25 g/kg 2DG injection. (E) time courses of the $R_{1\rho}$ change from the tumor and the contralateral tissue shows a faster and larger rise in the tumor region. The gray bars indicate the injection periods.

Fig. 4. GlucoCESL data with 0.5 g/kg Glc injections are qualitatively similar to those of 1 g/kg in Fig. 3 and show a linear dose-dependence. The gray bars indicate the injection periods.

Fig. 5.

Comparison of the initial period of the $R_{1\rho}$ time courses with that of DCE in the tumor.

(A) DCE time course (n = 4). (B) The rising periods of the $R_{1\rho}$ time courses from 1 g/kg of Glc and 0.25 g/kg of 2DG injections were fitted to Sigmoid functions. (C) the normalized time courses show that DCE has the fastest time to peak, while 2DG has the slowest. (D) Comparison of the 10 to 90% rise time for DCE MRI and CESL with L-Glc, Glc, and 2DG injections. *: p<0.05, **: p<0.01.

Table 1

List of the injections to individual animals

	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
0.5g/kg Glc	x	x	x	x	x							
1 g/kg Glc						x	x	x	x			
2DG	x	x	x				x		x	x		
L-Glc					x			x			x	x
Gd-DTPA				x	x		x			x		