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A Simple Method for Quantitative Measurement and Analysis of Hyperpolarized ^{129}Xe Uptake Dynamics in Mouse Brain under Controlled Flow

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We established a simple method for measuring and quantifying uptake dynamics of hyperpolarized (HP) ^{129}Xe in mouse brain, which includes application of a saturation recovery pulse sequence under controlled flow of HP ^{129}Xe . The technique allows pursuit of the time-dependent change in ^{129}Xe nuclear magnetic resonance signal in the uptake process without effect from radiofrequency destruction of the polarization and the dynamics in mouse lung. The uptake behavior is well described by a simple model that depends only on a decay rate constant comprising cerebral blood flow and the longitudinal relaxation rate of HP ^{129}Xe in the brain tissue. The improved analysis enabled precise determination of the decay rate constant as $0.107 \pm 0.013 \text{ s}^{-1}$ ($\pm$ standard deviation, $n = 5$), leading to estimation of longitudinal relaxation time, T_{1i} , as $15.3 \pm 3.5 \text{ s}$.

Keywords: *controlled flow, hyperpolarized ^{129}Xe , mouse brain, saturation recovery, uptake dynamics*

Introduction

Hyperpolarized (HP) ^{129}Xe holds great promise in analyses of brain function that utilize nuclear magnetic resonance (NMR) imaging and spectroscopy (MRI/MRS).^{1–7} Once HP ^{129}Xe dissolves in the pulmonary blood, it diffuses freely into the brain and produces an extraordinarily enhanced NMR signal that has up to 10^5 times' higher sensitivity than the signal of thermally polarized ^{129}Xe . Its use permits determination of unique brain function parameters, such as longitudinal relaxation time in the brain tissue (T_{1i}) as well as global and regional cerebral blood flow (gCBF/rCBF).^{8,9} Because T_{1i} is related to important physiological parameters, such as level of oxygenation and local temperature in brain tissue,^{10–12} it can become a novel parameter for evaluating brain function.

The dynamics in brain tissue of uptake and/or washout of HP ^{129}Xe have been successfully pursued by time-dependent change in dissolved-phase NMR signal intensity,^{13–17} and those researchers have proposed theoretical models to analyze the dynamics and determine the value of T_{1i} . However,

the analyses revealed that the dynamics are also affected by additive parameters, such as respiration rate and pulmonary blood flow, which are the input function of the analysis, and depolarization by radiofrequency (RF) excitation pulses.^{8,9,14} Difficulty separating these parameters from the T_{1i} and CBF analysis complicated interpretation of the dynamics. Accordingly, the T_{1i} values determined ranged widely (3.6 to 26 s).^{13–17} Therefore, satisfactory results are not obtained at present in the analysis of brain function using HP ^{129}Xe .

We previously proposed an effective experimental procedure to measure uptake and washout dynamics in the mouse brain under controlled flow of HP ^{129}Xe ,¹⁵ and we proved that HP ^{129}Xe 's dynamic behavior in brain tissue can be treated by a simple kinetic theory under this condition, thereby improving analysis. However, inevitable ambiguities in the analysis resulted from the dynamics of HP ^{129}Xe in lung and RF depolarization effect. A methodology is needed to observe and determine the HP ^{129}Xe dynamics in the brain to overcome these ambiguities.

In the present study, we improved experimental conditions and developed a method unaffected by RF depolarization and dynamics in the lung. In this measurement, controlled flow of HP ^{129}Xe is effec-

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tively applied to detect the time-dependent change in the NMR signal in the uptake process that is dominated only by the parameters of T_{1i} and CBF.

Materials and Methods

Materials

We purchased xenon gas over 99.995% pure and including 26.4% natural abundance of ^{129}Xe from Japan Air Gases (Hyogo, Japan) and used potassium (EP grade, over 98%), sodium (reagent grade, over 99%), and rubidium (EP grade, over 99.5%) metals (Nacalai Tesque, Kyoto, Japan) without further purification.

Continuous-flow production of HP ^{129}Xe

We produced hyperpolarized ^{129}Xe utilizing a well-known spin-exchange optical pumping method that employs a home-built continuous-flow apparatus (Fig. 1).^{15, 18} We used a mixture of 70% xenon and 30% nitrogen as a source of the HP gas, which was hyperpolarized under atmospheric pressure. We placed a cylindrical glass cell (Pyrex polarizing cell, 6-cm diameter, 30-cm long) in the fringe field (about 12 mT) of a super-conducting NMR magnet (9.4T). A droplet of rubidium (about 0.2 g) was deposited into the cell in an oven equipped with a LEISTER Hotwind S heated-air blower (LEISTER Japan, Tokyo, Japan). We maintained the cell's temperature at about 110°C. Circularly polarized light was irradiated at 795 nm into the cell to per-

form the pumping using laser diode arrays FAP-DUO system (COHERENT Japan Inc., Tokyo) under 90-W output power. The mixture of 70% Xe and 30% N_2 gases was passed through a vessel containing K-Na alloy to dry it at the entrance of the polarizing cell. The gas mixture was steadily supplied to the cell at 24 mL/min to produce HP ^{129}Xe and subsequently delivered through a glass mask attached to the head of a mouse set in an NMR probe. In the mask, oxygen was mixed with the HP $^{129}\text{Xe}/\text{N}_2$ mixture at a rate of 12 mL/min just before inhalation to reduce destruction of the polarization. The mouse spontaneously inhaled a 47:20:33 volume mixture of Xe: N_2 : O_2 gases. The partial pressure of HP ^{129}Xe inhaled by the mouse was 125 mbar and of O_2 , 338 mbar.

Animals

We used 5 male ddY mice (aged 6 weeks; weighing 27 to 30 g) (Japan SLC, Inc., Shizuoka). All experimental procedures and animal care strictly conformed to our university's guidelines. We initially anesthetized each animal with an intraperitoneal injection of pentobarbital (50 mg/kg, Dainippon Pharmaceutical Inc., Osaka, Japan). After the mouse was placed into an NMR spectrometer, the anesthesia was maintained with 1.5% halothane (Sigma Aldrich Japan, Tokyo, Japan) carried by O_2 using a calibrated vaporizer, Halorex H-200 (Shinei Industries Inc., Saitama, Japan). During NMR measurements, the gas mixture containing HP

Fig. 1. Schematic representation of continuous-flow type apparatus to produce hyperpolarized ^{129}Xe .

^{129}Xe , N_2 , and O_2 was continuously supplied to the masked mouse at the regulated flow rate. After NMR measurement, we removed the mouse from the probe and tested the xenon's anesthetic effect by monitoring pulse rate and oxygen saturation for 10 min using a CANL-425SVA pulse oximeter (NeuroScience Inc., Tokyo, Japan) via a photo transducer pair placed on the hind paw as the gas mixture containing HP ^{129}Xe continued to be supplied to the mouse. Oxygen saturation typically was between 92% and 97% and did not degrade appreciably. The heart rate also remained relatively constant throughout inhalation of the gas mixture.

NMR methods

We performed all experiments on a Varian Unity INOVA 400WB with a 9.4T vertical magnet (Varian Technologies Japan Ltd., Tokyo) and utilized a self-shielded imaging probe (Litz coil switchable to ^{129}Xe , ^1H , and ^{19}F) of 32-mm diameter equipping an RF coil 15-mm long (Doty Scientific, Columbia, SC, USA).

We applied a 3-part saturation recovery pulse sequence (Fig. 2) to measure the dynamics of uptake of HP ^{129}Xe in the brain under controlled flow. First, in a destruction phase, the HP ^{129}Xe magnetizations dissolved in the brain tissue, and a repetition of chemical-shift-selective 90° RF pulses destroyed the dissolved-phase HP ^{129}Xe . Then, during a variable recovery period of τ , the dissolved-phase HP ^{129}Xe freshly diffused from arterial blood to the brain tissue and recovered toward a steady state in relation to the parameters of T_{1i} and CBF. Finally, a hard 90° RF pulse was applied to detect the HP ^{129}Xe NMR signal at a given time point of τ . The dissolved-phase HP ^{129}Xe fully recovered to a

steady state in a pre-delay time (PD), and the saturation recovery pulse sequence was applied repeatedly with varying τ .

Before all experiments, we examined the degree of polarization as previously described;¹⁹ typically, we obtained polarization of 5 to 10%. RF pulse was calibrated by a “dual flip angle method” using a sealed glass tube phantom containing HP ^{129}Xe .²⁰

The mouse was anesthetized, placed in an animal container, set into the image probe with its head fixed at the center of the RF coil, and administered continuous HP ^{129}Xe during NMR measurements. Prior to the dynamics measurement, we acquired NMR spectra for at least 3 min to ensure that the concentration of the dissolved-phase HP ^{129}Xe reached steady state. Subsequently, we acquired the dynamic HP ^{129}Xe NMR spectra by repeatedly applying a saturation recovery pulse sequence in which the duration of τ was increased monotonically. To validate the accuracy of the present method, we applied 2 different experimental conditions to each mouse and compared results; 2 scans were accumulated for each τ (Condition 1: number of transients [nt]=2; increment of τ [$\Delta\tau$]=1.0 s; Condition 2: nt=1, $\Delta\tau$ =1.0 s). We repeated measurements at least 3 times for each experimental condition.

Typical measurement parameters were: spectral band width=82304.5 Hz; 49436 data complex points; 90° RF pulse length; and $1000\mu\text{s}$ for the chemical-shift-selective sinc pulse with an excitation width of 2500 Hz (equivalent to approximately 25 ppm) and $75\mu\text{s}$ for the hard pulse. The center frequency of the RF pulses was set at the dissolved-phase HP ^{129}Xe signal (196 ppm). Numbers of acquired spectra were 20 to 30, and pre-delay time was 3 s. The data were multiplied by a 20-Hz Lorentzian window function. Chemical shifts were referenced to the ^{129}Xe gas signal from the mask at 0 ppm.

^{129}Xe uptake model

In the present study, we derived a model suitable for analyzing the dynamics of HP ^{129}Xe uptake in brain tissue under the above-mentioned conditions.^{8,15}

After starting ventilation of HP ^{129}Xe with the inhaled concentration (C_i), the concentration of HP ^{129}Xe within the alveoli (C_A) depends on longitudinal relaxation time (T_{1A}) within the alveoli and on uptake by blood with a pulmonary blood flow (Q) and is given by Eq. (1):

$$\frac{dC_A(t)}{dt} = \frac{C_i R_F}{V_A} - \frac{C_A}{V_A} \left(R_F + \frac{V_A}{T_{1A}} + \lambda Q \right),$$

Fig. 2. Saturation recovery pulse sequence for measuring hyperpolarized (HP) ^{129}Xe uptake dynamics. The sequence is separated into 3 segments (detailed in Materials and Methods). In the first segment, Z crusher gradient (2 G/cm in strength, 2 ms in duration) was applied to dephase the chemical shift selectively excited HP ^{129}Xe magnetization in mouse brain. The repetition number (n) was three.

where R_F is a constant rate of gas exchange by breathing with an alveolar volume (V_A), and λ is the partition coefficient for Xe between the blood and the gas. In a steady state condition, one can obtain Eq. (2):

$$C_A = \frac{C_i R_F}{R_F + \frac{V_A}{T_{1A}} + \lambda Q}$$

The concentration of HP ^{129}Xe in the arterial blood that reaches the brain tissue (C_a) is expressed as Eq. (3):

$$C_a = \lambda C_A e^{-t_i/T_{1B}},$$

where T_{1B} is the longitudinal relaxation time in the blood and t_i is the time required for the blood to reach the brain tissue.

After its complete destruction, depending on the duration of τ , the dissolved-phase HP ^{129}Xe magnetization recovers to an amount, $C_i(\tau)$, the concentration of HP ^{129}Xe in the brain tissue. From Fick's principle, the change of HP ^{129}Xe in the brain tissue is expressed as Eq. (4):

$$\frac{dC_i(\tau)}{dt} = F_i C_a - \left(\frac{F_i}{\lambda_i} + \frac{1}{T_{1i}} \right) C_i,$$

where F_i is the gCBF (measured in mL of blood per mL of tissue per minute), λ_i is the partition coefficient between the tissue and blood, and T_{1i} is the longitudinal relaxation time in the brain tissue.

The time-dependent change of ^{129}Xe NMR signal amplitude on τ , $S(\tau)$, can be derived by solving Eq. (4) for the initial condition as $C_i(0) = 0$, and is given by Eq. (5):

$$S(\tau) = \eta C_i(\tau) = \frac{\beta}{\alpha} (1 - e^{-a\tau})$$

with $\alpha = \frac{F_i}{\lambda_i} + \frac{1}{T_{1i}}$, $\beta = \eta F_i \lambda C_A e^{-t_i/T_{1B}}$,

where η is the parameter that normalizes the concentration of HP ^{129}Xe in the brain tissue to the NMR signal amplitude.

Results

Figure 3 shows a typical NMR spectrum of HP ^{129}Xe obtained from the brain of Mouse 1. In the present study, we observed a single dominant peak at $196 (\pm 2)$ ppm for all measurements and weak signals around 190 ppm and 198 ppm. According to the literature, the main HP ^{129}Xe signal dissolved in the rat brain appears at around 196 ppm; the peak around 190 ppm originates from non-brain tissue.^{21,22} In accordance with the reported result, the MR image of HP ^{129}Xe acquired by chemical-

Fig. 3. Typical nuclear magnetic resonance (NMR) spectrum of hyperpolarized ^{129}Xe obtained from the mouse brain.

Fig. 4. Representative nuclear magnetic resonance (NMR) spectra of ^{129}Xe uptake dynamics in the mouse brain measured by the saturation pulse sequence under the controlled-flow condition. The corresponding τ value is also included.

shift-selection around 196 ppm accorded quite well with that of the entire region of the mouse brain in ^1H scout image, indicating that the signal originates from the brain parenchyma.²³ Therefore, in the present study, the main peak at around 196 ppm was assigned to the dissolved-phase HP ^{129}Xe originating from the mouse brain tissue. The origin of the peak at around 198 ppm is still unknown and needs to be determined in the future.

Figure 4 illustrates representative time-dependent change of the HP ^{129}Xe NMR signal on τ measured by means of the saturation recovery pulse sequence under controlled flow (Mouse 4, Condition 1); it is apparent that sufficient signal amplitudes and numbers of data points were obtained for analysis.

Figure 5 shows a representative profile of the HP ^{129}Xe uptake dynamics obtained from the brain of Mouse 5. In this analysis, we used a peak amplitude

Fig. 5. Representative time-dependent changes of nuclear magnetic resonance (NMR) signal amplitudes on τ . The filled circle corresponds to the observed NMR signal amplitude and the line is the fitting result.

Table. Decay rate constant, α , obtained from analysis of hyperpolarized ¹²⁹Xe uptake dynamics^a

Mouse	α (s ⁻¹)		
	Condition 1	Condition 2	Average ^b
1	0.091(0.006)	0.082(0.008)	0.087(0.010)
2	0.105(0.005)	0.136(0.011)	0.121(0.012)
3	0.090(0.007)	0.133(0.009)	0.112(0.011)
4	0.135(0.009)	0.083(0.008)	0.109(0.012)
5	0.106(0.006)	0.112(0.010)	0.109(0.012)
Average ^c	0.105(0.018)	0.109(0.026)	0.107(0.013)

^a Standard deviations given in parentheses.

^b Intra-animal average obtained from the values of 2 conditions.

^c Inter-animal average obtained from 5 mice.

at 196 ppm, as mentioned. The decay rate constant, α , was determined by nonlinear least-square fitting of the theoretical model described in Eq. (5) to the observed profile. The result of the fitting process is also included in Fig. 5. Table lists the α values of the 5 mice for the 2 experimental conditions. An inter-animal average α was obtained as 0.107 ± 0.013 s⁻¹ ($\pm$ standard deviation [SD], $n = 5$).

With knowledge of λ_i and F_i , the α value can be used to estimate T_{li} . The λ_i value was evaluated as 0.76 based on the method described in reference²⁴ with hematocrit of 47% and temperature of 37°C. In mouse brain, the value of F_i was reported as 1.76 ± 0.22 (mL blood/g tissue/min).²⁵ Assigning these values to Eq. (5), the T_{li} value could be estimated as 15.3 ± 3.5 s in the present study.

Discussion

We successfully measured and analyzed the uptake process of HP ¹²⁹Xe in the mouse brain utilizing a saturation recovery pulse sequence under controlled flow. In these measurements and analyses, it should be emphasized that the knowledge of the input function, which is the HP ¹²⁹Xe dynamics in the lung, is unnecessary because the concentration of HP ¹²⁹Xe in the lung is in a steady state and becomes constant under controlled flow (Eq. 2). As a result, the uptake of ¹²⁹Xe in the mouse brain was independent of the fluctuation of the input function and well described by the simple model (Eq. 5).

Furthermore, it should be noted that we pursued the uptake dynamics by irradiating 90° RF pulses, which resulted in sufficient NMR signal amplitudes and numbers of data points. In this measurement, the effect of RF depolarization within the brain tissue can be neglected because the HP ¹²⁹Xe magnetizations in the arterial blood are also constantly in a steady state and start to diffuse to the brain tissue immediately after the destruction phase of the pulse sequence. That is, the measured signal amplitude is directly proportional to the concentration of the HP ¹²⁹Xe dissolved in the brain tissue at a given time point, τ . Accordingly, it was possible not only to use 90° RF pulse as a detection pulse but also to accumulate the signals at a specific time point of τ . The validity of the idea is confirmed from the fact that the α values obtained for the 2 different experimental conditions almost correspond (Table) and are comparable to our previous data.¹⁵ This idea may be similar to the method proposed by Månsson's group²⁶ that enabled use of a 90° RF pulse to observe dynamic NMR spectra of HP ¹²⁹Xe in rat lung parenchyma.

Thus, the signal-to-noise ratio (SNR) of the dynamic NMR spectra obtained in the present study was improved greatly over that of the previous study¹⁵, in which a repetition of RF excitation with a small flip angle was used to minimize depolarization. The average maximum SNR values were 68 ± 13 for Condition 1 and 51 ± 7 for Condition 2, and the former, in which 2 scans were accumulated, was about $\sqrt{2}$ times larger than the latter, as expected. These SNR values are comparable to the best results measured in rat brains^{16,17} although the volume of the mouse brain is much smaller than that of rat. In these contexts, our simple method is probably superior to the previous methods.¹⁴⁻¹⁷

Zhou and associates pointed out that T_{li} analysis is very sensitive to SNR and suggested that low SNR unfavorably affects T_{li} analysis of HP ¹²⁹Xe.¹⁷ Therefore, the accuracy and reproducibility of the

present results have merit. When carefully comparing standard deviations of repeated measurements within and across the 5 mice for the 2 experimental conditions (Table), the relative standard deviations within the mice (4.6 to 7.8% for Condition 1) are better improved than those for Condition 2 (6.8 to 9.8%) ($P < 0.05$). This improved reproducibility within the mouse probably results from the improved SNR of the dynamic NMR spectra in Condition 1, supporting Zhou's suggestion. However, the SNR in Condition 2 is still comparable to the best results in rats. As a result, sufficient accuracy of the average α value across the mice might be obtained even in Condition 2, and consistency between the 2 conditions is observed. The improved accuracy of the analysis made it possible to determine precisely the decay rate constant, α , as $0.107 \pm 0.013 \text{ s}^{-1}$, leading to an estimation of T_{1i} of mouse brain as $15.3 \pm 3.5 \text{ s}$. The relevance of this estimation is confirmed by comparing it with our previous data (14 s).¹⁵

One drawback of the present method is that it requires relatively time-consuming measurements. Because the measurements take at least 3 min even in experimental Condition 2, the anesthetic effect of xenon may cause a change in physiological states. This may become a problem in the clinical application of the method although a change in physiological state of the mouse was not observed in the present study. To solve this problem, we are developing a fast version of this method.

Conclusion

In this study, we have established a simple and robust method for measuring and analyzing the dynamics of HP ^{129}Xe uptake in mouse brain that avoids any effect of RF depolarization and dynamics in the lung. An important technique for this method was applying a saturation recovery pulse sequence under controlled flow. Our method enabled us to overcome the uncertainty that had existed in analyzing the brain dynamics of HP ^{129}Xe , which led to the precise determination of the decay constant. Thus, the accuracy in estimating longitudinal relaxation time, T_{1i} , of HP ^{129}Xe in mouse brain was greatly improved. Our method will be useful in future brain study.

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