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Off-Resonance Effects of the Radiofrequency Pulses Used in Spectral Editing with Double-Quantum Coherence Transfer

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Spectral editing using gradient selected double-quantum (DQ) coherence transfer is often used for the selective observation of metabolites *in vivo.* In attempting to optimize the detection sensitivity of a conventional DQ spectral editing sequence, the effects of using radiofrequency (RF) pulses that are not at the resonance frequency of the observed peaks were investigated both theoretically and experimentally. The results show that spectral editing using pulses at the frequency of the observed resonance does not necessarily give the optimal detection sensitivity. At 7 T, the detection sensitivity of lactate observed using a DQ editing method can be increased by up to 30% by setting the RF pulses off resonance at the proper frequency. The results also suggest that slice selective RF pulses used in DQ spectral editing combined with PRESS localization may have slice profiles different from those when the same pulses are used for standard PRESS spatial localization.

Key Words: **spectral editing; double quantum coherence transfer; double quantum filtering; magnetic resonance spectroscopy; lactate.**

INTRODUCTION

Spectral editing techniques using gradient selected double-quantum (DQ) coherence transfer provide a good compromise between fat and water suppression, detection sensitivity, and motion sensitivity for *in vivo* applications (*1, 2*). These techniques have been applied to the selective observation of a number of metabolites *in vivo,* including lactate (*3–5*), γ-aminobutyric acid (GABA) (*6, 7*), citrate (*8*), glucose (*9*), *N*-acetyl-aspartate (*10*), taurine (*11*), glutathione (*12*), and glutamate (*13*). However, unequivocal observation of a metabolite by DQ spectral editing is often at the cost of reduced sensitivity. Generally, only a fraction of the signals from the target metabolite can pass through a DQ editing sequence (*1*), and the signals passing through the sequence are attenuated further by mechanisms such as transverse relaxation, spin-diffusion, *J*-modulation, and radiofrequency (RF) pulse imperfections (*4*). Therefore, when DQ spectral editing is used to observe a metabolite with low concentration *in vivo,* it is not only essential for the sequence to be efficient in filtering out major overlapping resonances, but also important for the sequence to have optimized detection sensitivity for the metabolite of interest. A conventional DQ spectral editing sequence consists of five RF pulses and delays between the pulses (*1, 14*). Optimization of the detection sensitivity for a DQ metabolite editing sequence can be achieved by adjusting the timing of the sequence and by optimizing the settings for the RF pulses. Theoretical treatments using product operator formalisms or numerical simulation can be used to guide the optimization process (*2, 13, 15*).

The flip angles, durations, and shapes of the RF pulses in a DQ editing sequence all affect the detection sensitivity of the sequence (*13, 16, 17*). When point resolved spectroscopy (PRESS) spatial localization is combined with DQ spectral editing (*5, 6, 12, 13*), the frequency offset of the slice selective RF pulses used also affects the detection sensitivity (*5*). In this study, the effects of RF pulses that are not at the resonance frequency of the observed peak (i.e., off-resonance pulses) on the detection sensitivity of a conventional DQ spectral editing sequence are investigated.

THEORY

A conventional DQ editing sequence is shown in Fig. 1. The antiphase coherence is generated during the DQ creation period (2τ) and is then converted into DQ coherence by the second 90° pulse. After the DQ coherence evolution period (t_1), the third 90° pulse (i.e., the DQ read pulse) converts the DQ coherence back into single-quantum coherence which is then detected at the end of the detection period ($\tau_1 + \tau_2$). A frequency selective pulse is usually used for the DQ read pulse to increase the intrinsic detection sensitivity (*1, 18*). Consider a weakly coupled two-spin-$\frac{1}{2}$ system (IS) with a frequency difference ω_{IS} between the two spins. Using a product operator formalism in the spherical basis (*19*), the coherence transfer pathways involving the DQ coherence ($\mathbf{I}_+\mathbf{S}_+$) and leading to observable signals of spin I ($\mathbf{I}_-$) are

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$$\mathbf{I}_0 \xrightarrow{90^\circ} \mathbf{I}_- \xrightarrow{\tau} \mathbf{I}_-\mathbf{S}_0 \xrightarrow{180^\circ} \mathbf{I}_+\mathbf{S}_0 \xrightarrow{\tau} \xrightarrow{90^\circ} \mathbf{I}_+\mathbf{S}_+ \xrightarrow{t_1} \xrightarrow{90^\circ} \mathbf{I}_+\mathbf{S}_0 \xrightarrow{\tau_1} \xrightarrow{180^\circ} \mathbf{I}_-\mathbf{S}_0 \xrightarrow{\tau_2} \mathbf{I}_-$$

$$\mathbf{I}_0 \xrightarrow{90^\circ} \mathbf{I}_+ \xrightarrow{\tau} \mathbf{I}_+\mathbf{S}_0 \xrightarrow{180^\circ} \mathbf{I}_-\mathbf{S}_0 \xrightarrow{\tau} \xrightarrow{90^\circ} \mathbf{I}_+\mathbf{S}_+ \xrightarrow{t_1} \xrightarrow{90^\circ} \mathbf{I}_+\mathbf{S}_0 \xrightarrow{\tau_1} \xrightarrow{180^\circ} \mathbf{I}_-\mathbf{S}_0 \xrightarrow{\tau_2} \mathbf{I}_-,$$

where $\mathbf{I}_0$ and $\mathbf{S}_0$ represent the longitudinal magnetization of spins I and S, respectively, and $\mathbf{I}_-\mathbf{S}_0$ and $\mathbf{I}_+\mathbf{S}_0$ represent the antiphase coherence.

The effects of an off-resonance pulse with a frequency offset $\Delta\omega_I$ (relative to the on-resonance frequency of I) on I can be described as (*20*)

$$\mathbf{I}_- \xrightarrow{\beta,\phi,\theta} \frac{\mathbf{I}_-}{2}\{[\cos\beta(1+\cos^2\theta)+\sin^2\theta] + 2i\sin\beta\cos\theta\} + \frac{\mathbf{I}_0}{\sqrt{2}}\exp(-i\phi)\times\left[\sin^2\left(\frac{\beta}{2}\right)\sin 2\theta - i\sin\beta\sin\theta\right] + \frac{\mathbf{I}_+}{2}\exp(-2i\phi)[(\cos\beta-1)\sin^2\theta] \quad [1]$$

$$\mathbf{I}_+ \xrightarrow{\beta,\phi,\theta} \frac{\mathbf{I}_+}{2}\{[\cos\beta(1+\cos^2\theta)+\sin^2\theta] - 2i\sin\beta\cos\theta\} + \frac{\mathbf{I}_0}{\sqrt{2}}\exp(i\phi)\left[-\sin^2\left(\frac{\beta}{2}\right)\sin 2\theta - i\sin\beta\sin\theta\right] + \frac{\mathbf{I}_-}{2}\exp(2i\phi)[(\cos\beta-1)\sin^2\theta] \quad [2]$$

$$\mathbf{I}_0 \xrightarrow{\beta,\phi,\theta} \frac{\mathbf{I}_+}{\sqrt{2}}\exp(-i\phi)\left[-\sin^2\left(\frac{\beta}{2}\right)\sin 2\theta - i\sin\beta\sin\theta\right] + \mathbf{I}_0(\cos\beta\sin^2\theta+\cos^2\theta) + \frac{\mathbf{I}_-}{\sqrt{2}}\exp(i\phi)\times\left[\sin^2\left(\frac{\beta}{2}\right)\sin 2\theta - i\sin\beta\sin\theta\right] \quad [3]$$

$$\beta = \sqrt{(\gamma B_1)^2 + \Delta\omega_I^2}\times t_p \quad [4]$$

$$\theta = \mathrm{atan}(\gamma B_1/\Delta\omega_I), \quad [5]$$

where β is the effective flip angle of the RF pulse, ϕ is the phase of the pulse, θ is the tip angle away from the z axis (i.e., $\theta = \pi/2$ for an on-resonance pulse), γ is the gyromagnetic ratio, B_1 is the RF amplitude, and t_p is the duration of the pulse. Equations similar to Eqs. [1] to [5] can also be written for spin S. Note that the frequency offset of the same RF pulse for S is $\Delta\omega_S = \Delta\omega_I + \omega_{IS}$, and consequently β and θ for S are different from those for I.

Normally, when I is edited, the frequency of all the RF pulses in the pulse sequence is set on resonance for I, except for the DQ read pulse whose frequency is set on resonance for S. Now, consider the last 180° pulse in the sequence, which converts the antiphase coherence $\mathbf{I}_+\mathbf{S}_0$ to $\mathbf{I}_-\mathbf{S}_0$. In order to obtain 100% conversion efficiency, this pulse must act as a perfect refocusing pulse for I (i.e., converting $\mathbf{I}_+$ to $-\mathbf{I}_-$), and simultaneously as a perfect inversion pulse for S (i.e., converting $\mathbf{S}_0$ to $-\mathbf{S}_0$). This requires the pulse be on resonance for both I and S. However, in practice, this will not be the case. In general, a real 180° pulse will convert $\mathbf{I}_+\mathbf{S}_0$ into $\mathbf{I}_-\mathbf{S}_0$ with a conversion efficiency factor E_{180} (see Eqs. [1] to [5]),

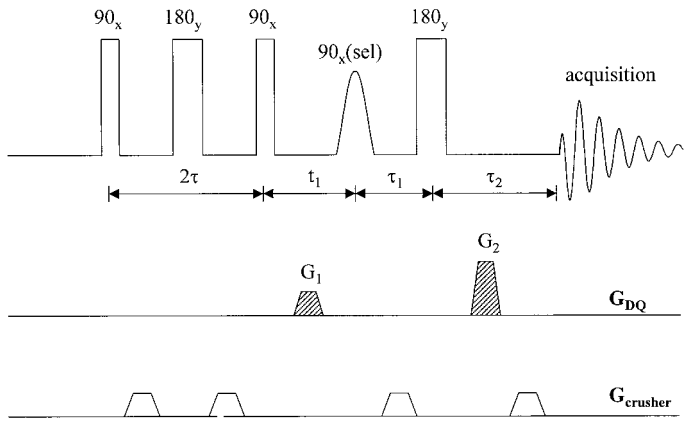

FIG. 1. A pulse sequence for spectral editing using double-quantum coherence transfer.

$$\mathbf{I}_+\mathbf{S}_0 \xrightarrow{180^\circ} E_{180} \times \mathbf{I}_-\mathbf{S}_0$$

$$= \frac{(\cos\beta_I - 1)\sin^2\theta_I}{2}(\cos\beta_S\sin^2\theta_S + \cos^2\theta_S)\mathbf{I}_-\mathbf{S}_0, \quad [6]$$

where the subscripts I and S represent the spins I and S, respectively. The value of E_{180} depends upon experimental parameters such as B_1, t_p, and $\Delta\omega_I$ as well as the properties of the spin system such as ω_{IS}. Due to the existence of ω_{IS}, the maximum value of E_{180} does not necessarily occur when the pulse is on resonance for I (i.e., $\Delta\omega_I = 0$). In analogy to Eq. [6], it is possible to derive a conversion efficiency factor for each RF pulse in the sequence using Eqs. [1] to [5]. The product (E_c) of the conversion efficiency factors from all pulses then gives the overall off-resonance effect. Optimizing the detection sensitivity of a DQ editing sequence involves determining the value of $\Delta\omega_I$ that gives the best value for E_c.

MATERIALS AND METHODS

All experiments were carried out on a Bruker Biospec/3 spectrometer using a 7 T/21 cm magnet equipped with actively shielded gradients. A homebuilt 3-cm-diameter saddle coil was used for both transmission and reception. The on-resonance flip angles of all pulses were carefully calibrated (*21*), and the orientations of all crusher gradients ($G_{crusher}$) and coherence transfer pathway selection gradients (G_{DQ}) were adjusted experimentally to a near-magic-angle setting to maximize the efficiency of water/solvent suppression (*22*).

Experiments were performed using two 2.5-cm-diameter vial phantoms. Phantom I contained 50 mM 5-bromo-2-furoic acid (BFA) in 20/80 dimethyl sulfoxide benzene. The frequency difference between the H4 and H3 protons of BFA was 276 Hz. Phantom II contained 20 mM each of lactate, choline, GABA, and taurine in saline solution. All experiments used hard pulses as the 90° pulses (except for the DQ read pulse). With phantom I, DQ editing for H4 and H3 of BFA was performed as the frequency offset of the last 180° pulse varied from −1600 Hz (e.g., upfield) to 1600 Hz (e.g., downfield) with respect to the resonance frequency in each case. DQ editing was carried out at two RF power levels adjusted to give a 180° hard pulse of 150 or 260 μs. Using phantom II and a hard 180° pulse of 260 μs, spin echo and inversion recovery spectra of water were acquired as the frequency offset of the refocusing pulse or the inversion pulse varied from −2400 to 2400 Hz with respect to the resonance frequency of water. Spin echo spectra of water were also acquired using a 2-ms three-lobe sinc pulse as the refocusing pulse, with the frequency offset of this pulse varying from −1600 to 1600 Hz with respect to the water resonance. Spectral editing for the methyl protons of lactate and γ-protons of GABA was also performed on phantom II, as the frequency offset of a single RF pulse or a combination of the RF pulses was varied from −1600 to 1600 Hz with respect to the observed resonance in each case. GABA editing was carried out with hard 180° pulses of 260 μs. Lactate editing was done using hard pulses of 260 μs or three-lobe sinc pulses of 1 or 2 ms as the 180° pulses. All flip angles were calibrated with the carrier frequency on resonance for the observed peak.

The spin echo and inversion recovery spectra were acquired with a repetition time (TR) of 6.0 s, a spectral bandwidth of 5000 Hz, 2048 data points, and 8 averages. The echo time (TE) was 40 ms and the inversion recovery time (TI) was 20 ms. DQ edited spectra were acquired with the pulse sequence shown in Fig. 1, with TR = 6.0 s, t_1 = 8.0 ms, a spectral bandwidth of 6024 Hz, 2048 data points, and 8 averages. For lactate, GABA, and BFA editing, 2τ was 40.8, 34, and 120 ms, respectively. The detection periods τ_1 and τ_2 were set to $\tau - t_1$ and $\tau + t_1$, respectively, in order to simultaneously refocus the coherence transfer echo and the B_0 inhomogeneity. A 12-ms single-lobe sinc pulse with a flip angle of 90° was used as the DQ read pulse. To edit for H3 and H4 of BFA, the frequency of the read pulse was centered on the H4 and H3 resonances, respectively. For lactate and GABA editing, the frequency of the read pulse was centered on the methine resonance of lactate and the β-proton resonance of GABA, respectively. Postacquisition spectral processing in all cases included zero-filling the free induction decays to 4096 data points and applying a 5-Hz exponential line-broadening. Spectra were phased individually to give a pure absorption lineshape. Peak height was used for quantification after verifying that the linewidths and lineshapes remained constant throughout the experiment.

RESULTS

Figure 2a shows the changes in the water signal intensity as the frequency offset of the refocusing pulse was varied in the spin echo experiment, and Fig. 2b shows the amount of longitudinal magnetization inverted as the frequency offset of the inversion pulse was varied in the inversion recovery experiment, using hard 180° pulses of 260 μs. The solid lines in the figure were simulated from the relevant terms in Eqs. [2] and [3], respectively, and provide excellent fits to the experimental data.

The results of spectral editing for H3 and H4 of BFA are shown in Fig. 3. The data were acquired as the frequency offset of the last 180° pulse in the pulse sequence shown in Fig. 1 was varied and with hard 180° pulses of 150 μs (Fig. 3a) and 260 μs (Fig. 3b), respectively. The solid lines in the figure were simulated using Eq. [6] and fit the experimental data very well in each case. For both the experimental data and the theoretical curves, the maxima are displaced from the resonance frequency of the observed proton in each case to approximately midway between the H3 and H4 resonance frequencies. As

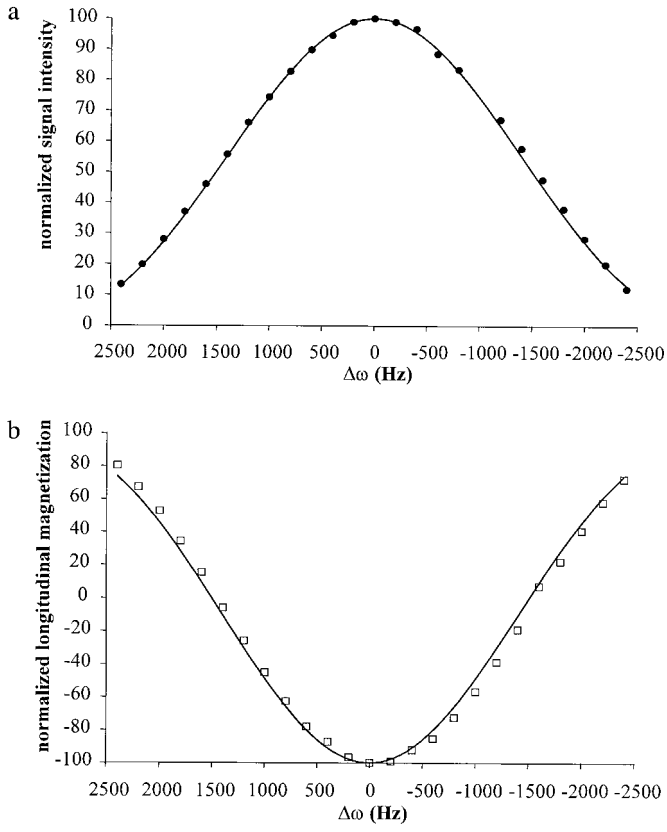

FIG. 2. The dependence of the water ^{1}H MR signal intensity on the frequency offset of the refocusing pulse in a spin echo experiment (a) and the dependence of the inverted longitudinal magnetization on the frequency offset of the inversion pulse in an inversion recovery experiment (b). The solid lines are theoretical simulations from the relevant terms in Eqs. [2] and [3], respectively.

the RF power decreases and the 180° pulse length increases, the envelope functions described by Eq. [6] become narrower (Fig. 3b).

Figure 4 shows the dependence of the edited lactate signal intensity on the frequency offset of each individual RF pulse in the pulse sequence shown in Fig. 1. The dotted lines in the figure connect the data points. A periodic modulation resembling a sin/cos function for the edited signal intensity with respect to the frequency offset is apparent for the first 90° pulse and for the first 180° pulse, but not for the second 90° pulse or the second 180° pulse. For both 180° pulses, the edited signal intensity is also modulated with an envelope function similar to that observed in BFA editing. The maximum for this envelope function occurs when the frequency of the RF pulse is shifted by about 450 Hz (i.e., about 1.5 ppm) toward the lactate methine resonance and has an intensity that is about 11% higher than that when the pulse is on resonance for the lactate methyl protons.

In Fig. 5, the closed squares (lactate) and circles (GABA) show the effects on the edited signal intensity of changing the frequency offset of the last 180° pulse, and the crosses (lactate) and asterisks (GABA) show the effects on the edited signal intensity of changing the frequency offset of *all* of the RF pulses (except for the DQ read pulse) simultaneously by the same amount. The dotted lines in the figure connect the data points. When the frequency offset of *all* of the pulses was changed synchronously, the envelope functions become narrower, showing that the effects of the off-resonance RF pulses are cumulative. The maximum edited signal intensity occurs at a frequency offset of about 450 Hz for lactate editing and at a frequency offset of about −200 Hz for GABA editing and is higher by about 30% for lactate and 8% for GABA compared to that observed when the RF pulses are set on resonance for the observed protons.

The experimental envelope functions when 1- or 2-ms three-lobe sinc pulses were used as the 180° pulses for DQ lactate editing and the frequency offset of the second 180° pulse was varied are shown in Fig. 6. Both envelope functions are dis-

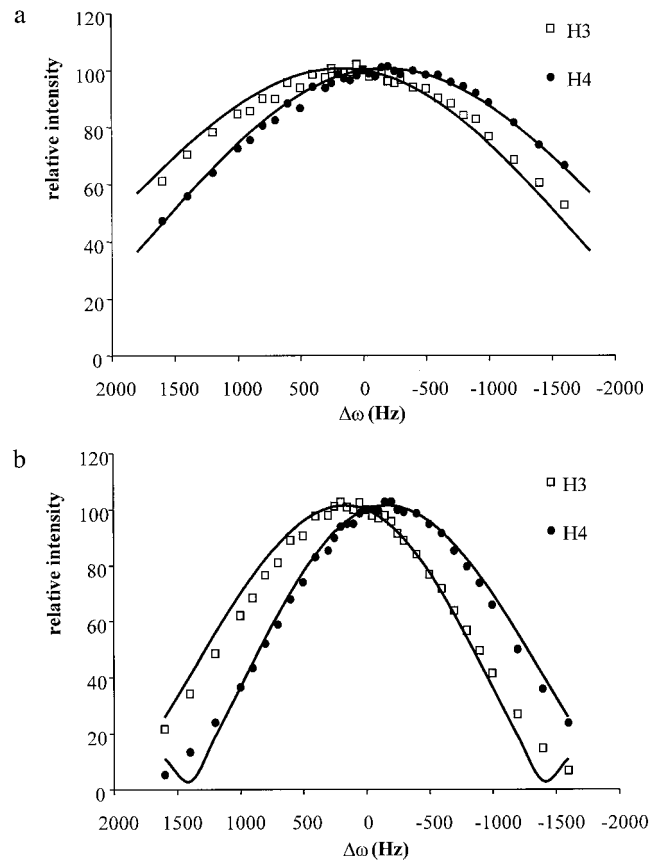

FIG. 3. The dependence of the edited ^{1}H MR signal intensities of 5-bromo-5-furoic acid on the frequency offset of the last 180° pulse in the pulse sequence shown in Fig. 1. Data in a and b were acquired with hard 180° pulses of lengths 150 and 260 μs, respectively. In both a and b, the open boxes represent the experimental data from editing for H3, and the closed circles represent the experimental data from editing for H4. The solid lines are theoretical simulations using Eq. [6].

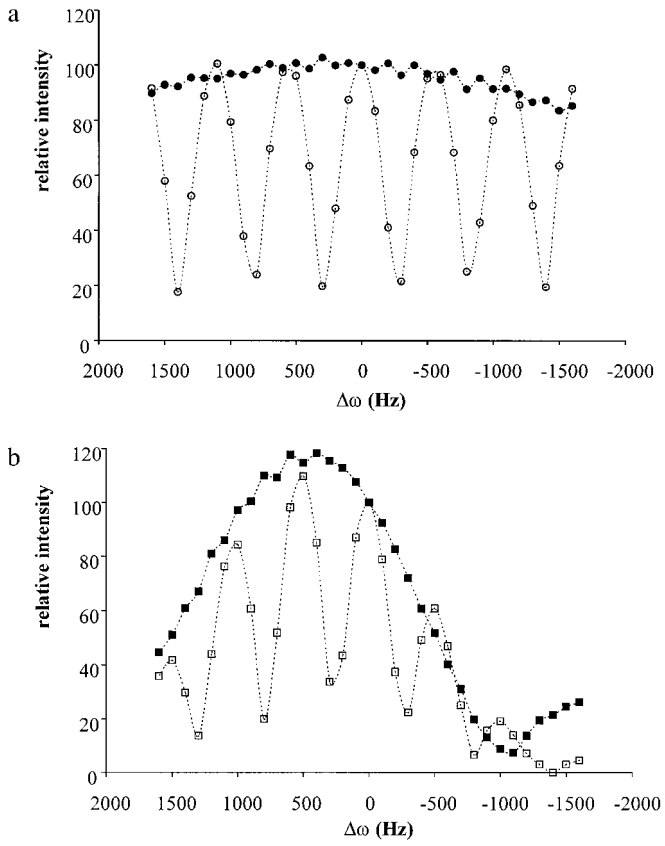

FIG. 4. The dependence of the edited lactate signal intensity on the frequency offset of the first (open circles) and the second (closed circles) 90° pulses (a) and of the first (open squares) and the second (closed squares) 180° pulses (b) in the pulse sequence shown in Fig. 1.

placed relative to the lactate methyl proton resonance frequency. Figure 7 compares the experimental envelope functions for a 2-ms three-lobe sinc pulse when it is used as the refocusing pulse in a simple spin echo experiment and in a DQ editing experiment. Although the two envelope functions have essentially the same overall bandwidth (i.e., −1400 to 1400 Hz), they differ markedly in shape. In the spin echo experiment, the envelope function is symmetrical, with the shape typically seen for a sinc pulse. However, in the DQ editing experiment, the envelope function has an irregular shape, showing that there is nonuniform refocusing across the frequency range covered by the pulse. The dotted lines in both Fig. 6 and Fig. 7 connect the data points.

DISCUSSION

The off-resonance effect of a 90° excitation pulse has been described experimentally (*23*) and treated theoretically (*24*). In the present study, the off-resonance effect of an RF pulse is examined in a DQ spectral editing sequence for the selective

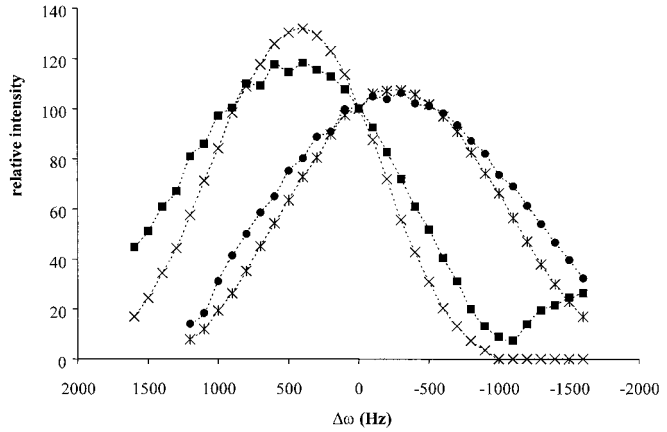

FIG. 5. The dependence of the edited lactate and GABA signal intensities on the frequency offset. Data points represented by closed squares (lactate) and circles (GABA) were acquired by varying the frequency offset of the last 180° pulse only. Data points represented by crosses (lactate) and asterisks (GABA) were acquired by varying the frequency offset of all four RF pulses (except for the DQ read pulse) simultaneously by the same amount.

observation of coupled spin systems. In a conventional DQ spectral editing sequence (Fig. 1), the RF pulses (except for the DQ read pulse) are not frequency selective and are designed to act on all the spins in the spin system. For coupled spin systems, especially for weakly coupled systems in which large chemical shift differences between the coupled spins exist, any RF pulse that is on resonance for one spin will be off resonance for the other spin(s). As a result, even though the non-frequency-selective RF pulses are *on resonance* for the observed spin, an off-resonance effect will still be introduced and can reduce the efficiency of the coherence transfer. The significance of this effect in any given experiment depends on the chemical shift difference between the spins and on the experimental param-

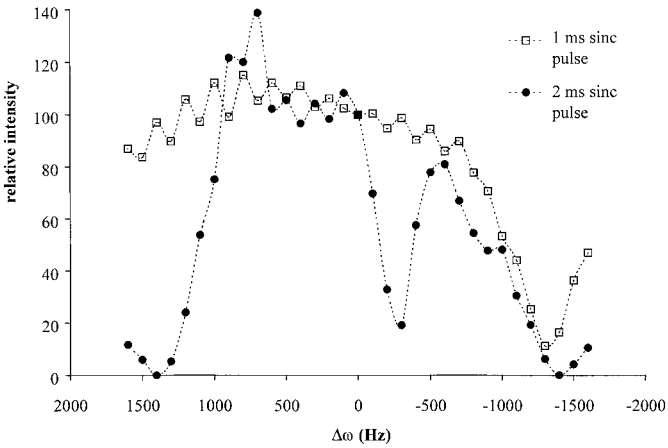

FIG. 6. The dependence of the edited lactate signal intensity on the frequency offset of the last 180° pulse in pulse sequence shown in Fig. 1 when three-lobe sinc pulses with duration of 1 or 2 ms were used as the 180° pulses.

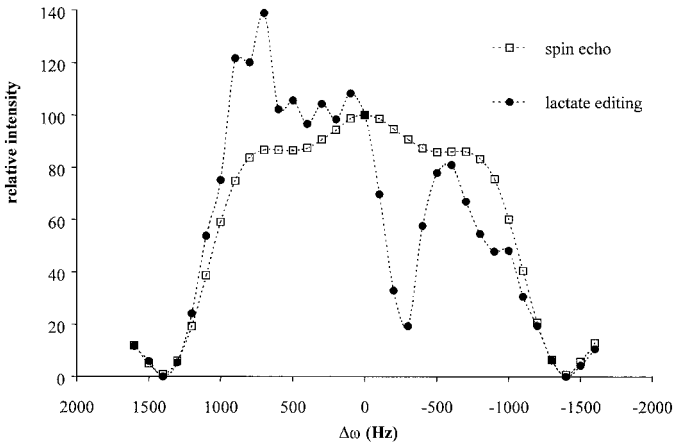

FIG. 7. Comparison of the offset-dependence functions of a 2-ms three-lobe sinc pulse when it is used as the refocusing pulse to observe the water resonance in a spin echo experiment and to observe the lactate methyl resonance in a DQ editing experiment.

eters such as the field strength, the RF power, and the length of the RF pulses. The off-resonance effect is more prominent at higher field and with a spin system having a larger chemical shift difference. The off-resonance effect is also related to the length of the RF pulses. Longer RF pulses usually have larger off-resonance effects (*23*). One implication of the off-resonance effect described here is that the optimum detection sensitivity in a DQ editing experiment is not necessarily obtained when all the RF pulses are *on resonance* for the observed spins. Thus, in this study, the detection sensitivity of edited lactate and GABA resonances was improved by up to 30 and 8%, respectively, by setting the RF pulses at an optimized off-resonance frequency (Fig. 5). This off-resonance effect is greater in editing for lactate than in editing for GABA because the chemical shift difference between the relevant coupled spins in lactate (2.8 ppm) is larger than that in GABA (1.1 ppm). The frequency offset giving the maximum detection sensitivity for a DQ metabolite editing sequence can be estimated theoretically from Eq. [6]. This optimum pulse frequency is always between the resonance frequencies of the two coupled spins which are involved in the spectral editing. Thus the maximum detection sensitivity for lactate is obtained when the frequencies of the excitation and refocusing pulses are centered at 2.7 ppm, almost halfway between the lactate methyl resonance (1.33 ppm) and the lactate methine resonance (4.10 ppm). At this position a single RF pulse most closely approximates the requirement of being on resonance for both spins simultaneously.

The first 90° excitation pulse and the two 180° pulses in a conventional DQ editing sequence can be switched from hard pulses to slice selective pulses to achieve three-dimensional PRESS spatial localization (*5*, *6*, *12*, *13*). However, the intensity of edited lactate signals observed using such a sequence is modulated by the frequency offset of the first 90° pulse and the first 180° pulse, but not by the frequency offset of the last 180° pulse (*5*). This has been attributed to phase accumulation of the off-resonance slice selective pulses during the switching of the synthesizer frequency (*5*) and is therefore due to hardware limitations. Phase calibration schemes have been suggested to solve this problem (*12*, *18*). A similar modulation of the intensity of the edited lactate signals was also observed in the present study (Figs. 4a and 4b). However, this intensity modulation caused by phase accumulation is distinctly different from the off-resonance effects inherent in the spin system described here. This is apparent from the offset-dependence profile of the first 180° pulse (Fig. 4b), which has a sin/cos-like modulation caused by phase accumulation along with modulation by an envelope function that results from the true off-resonance effect.

An important implication of the results obtained in this study is that caution must be exercised when DQ spectral editing is combined with PRESS spatial localization, even when phase calibration procedures are used. In a standard PRESS experiment, the two 180° pulses serve simply as refocusing pulses to refocus normal transverse magnetization. In DQ spectral editing, however, the two 180° pulses are involved in coherence transfer and act on the antiphase coherence. They thus serve simultaneously as refocusing pulses (for the observed spins) and inversion pulses (for the spin(s) that is coupled to the observed spins and involved in spectral editing). As a result, the offset-dependent envelope function of a shaped pulse when used in a DQ editing experiment is different from that when it is used in a standard PRESS experiment, as shown in Fig. 7. Then when a shaped pulse is used as a slice selective pulse in DQ editing combined with PRESS localization, the irregular shape of the offset-dependent envelope function of the pulse will result in an irregular slice profile that is different from the expected slice profile observed in a standard PRESS experiment. The slice profile of any slice selective RF pulse must therefore be confirmed and the performance in spatial localization must be assessed when combining PRESS with DQ editing.

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