NMR IN BIOMEDICINE
NMR Biomed **11,** 266–272 (1998)

Simultaneous *in vivo* spectral editing and water suppression

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Received 9 October 1997; revised 4 December 1997; accepted 13 January 1998

ABSTRACT: Water suppression is typically performed *in vivo* by exciting the longitudinal magnetization in combination with dephasing, or by using frequency-selective coherence generation. MEGA, a frequency-selective refocusing technique, can be placed into any pulse sequence element designed to generate a Hahn spin-echo or stimulated echo, to dephase transverse water coherences with minimal spectral distortions. Water suppression performance was verified *in vivo* using stimulated echo acquisition mode (STEAM) localization, which provided water suppression comparable with that achieved with four selective pulses in 3,1-DRYSTEAM. The advantage of the proposed method was exploited for editing *J*-coupled resonances. Using a double-banded pulse that selectively inverts a *J*-coupling partner and simultaneously suppresses water, efficient metabolite editing was achieved in the point resolved spectroscopy (PRESS) and STEAM sequences in which MEGA was incorporated. To illustrate the efficiency of the method, the detection of γ-aminobutyric acid (GABA) was demonstrated, with minimal contributions from macromolecules and overlying singlet peaks at 4 T. The estimated occipital GABA concentration was consistent with previous reports, suggesting that editing for GABA is efficient when based on MEGA at high field strengths. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: frequency selective water suppression; GABA; human brain; *in vivo* ^{1}H MRS

INTRODUCTION

^{1}H spectroscopy can provide detailed chemical information about human tissues, because of its high sensitivity.[1] To achieve consistently accurate quantification, high quality water suppression is necessary. Various frequency selective techniques have been used to achieve water suppression *in vivo*.[2–6]

Chemical shift selective suppression (CHESS),[2] and related water-suppression methods, use frequency selective prepulses followed by dephasing gradients to minimize the water *z*-magnetization prior to excitation. Since these methods are applied during a small time prior to excitation, the water signal may recover because of T_1 relaxation or spin exchange, and the overall pulse sequence time is somewhat increased. Several variations of CHESS have been introduced to further improve water suppression,[3,7–9] such as DRYSTEAM (DRY Stimulated Echo Acquisition Mode).[3] DRYSTEAM uses several frequency selective pulses combined with gradient dephasing, which are applied prior to the first slice selective pulse and during *TM* (see Fig. 2A), to optimize the suppression of a specific resonance. Modifications of CHESS, in which flip angles, pulse shapes, interpulse delays and/or dephasing gradient strengths are varied, can improve the suppression of a given resonance for a selected range of T_1 and B_1 values.[7–9] Empirical adjustments of several frequency selective pulse flip angles may be necessary to optimize water suppression.

Binomial pulses[10] and variants thereof, can also be used to achieve excellent water suppression as well as for spectral editing. For instance, spectral editing of lactate has been performed by subtracting the spectra acquired with a binomial refocusing pulse from the spectra acquired with a hard 180° pulse, which does not retain the full water-suppression capability.[11]

We described previously the new solvent-suppression sequence element MEGA,[12,13] which can be placed within any pulse sequence containing an element whose function is to refocus transverse magnetization. MEGA employs gradients surrounding the frequency selective ‘refocusing’ pulses to dephase transverse magnetization (as illustrated in Fig. 1 for a simple spin echo sequence). A detailed analysis and comparison of MEGA to related

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Contract/grant sponsor: NIH; *contract grant number:* RR08079 and CA64338.

Abbreviations Used: CHESS, chemical shift selective suppression; Cho, choline; Cr, creatine; DRYSTEAM, dry stimulated echo acquisition mode; GABA, γ-aminobutyric acid; MM, macromolecule; NAA, N-acetyl-aspartate; PRESS, point resolved spectroscopy; STEAM, stimulated echo acquisition mode.

CCC 0952–3480/98/060266–07 $17.50

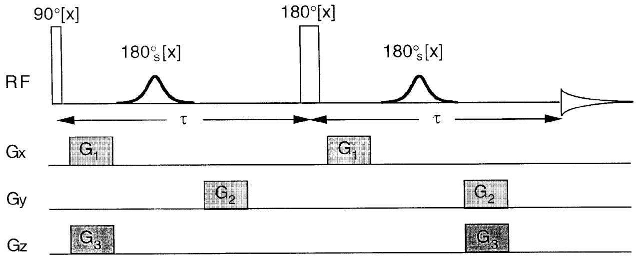

Figure 1. The RF pulses and gradient waveforms required for MEGA implemented in a Hahn spin echo sequence. The flip angle α_s of the frequency selective pulse is 180°. MEGA gradients are indicated by G_1, G_2 and G_3

methods[14–16] has been presented.[12] Through theoretical calculations and experimental validation, we demonstrated previously the following advantages of the sequence element MEGA: (1) It is relatively insensitive to pulse flip angle errors of the frequency selective pulses, because of RF field inhomogeneities or inaccurate pulse calibration; (2) MEGA does not introduce phase distortion to spectral peaks off resonance; (3) MEGA is easy to implement since the frequency selective pulses are identical (180°_s); (4) Inter-conversion of transverse and longitudinal magnetization does not occur when MEGA is used. Here, the performance of MEGA for water suppression is demonstrated in the simple Hahn spin echo and the stimulated echo acquisition mode (STEAM)[17] sequences.

Since MEGA water suppression relies on applying two 180°_s pulses about a refocusing pulse, it lends itself to be used for the editing of *J*-coupled spin systems. We demonstrate the resulting efficiency for editing, for GABA in the human brain using dual frequency editing pulses in the PRESS[18] and STEAM[17] sequences.

EXPERIMENTAL

To demonstrate this solvent-suppression scheme, MEGA was incorporated into a spin echo sequence (Fig. 1). The two frequency selective pulses (180°_s), with their carrier frequencies centered at the solvent resonance, surround the broadband 180° pulse. Asymmetrically placed gradients (G_1 and G_2) are used to dephase spins within the bandwidth of the selective pulses. The spoiler gradients on the third axis (G_3) are placed symmetrically around the 180° pulse which generates the primary Hahn spin echo. Spins outside the bandwidth of the frequency selective pulses are refocused by the broadband 180° pulse.

MEGA (Fig. 1) was tested using a 40 cm horizontal bore 4.7 T magnet (Oxford Insts. Ltd, Oxford, UK) with a custom-built 10.8 cm gradient coil interfaced to a Varian console (Varian, Palo Alto, CA). A linear birdcage RF coil was used to detect the signal from an 18 mm spherical water-filled phantom. The broadband 90° and 180° pulse lengths were 50 μs and 100 μs, respectively. For the 180°_s pulses, 5 ms Gaussian pulses were applied. Sine-shaped gradients with a half cycle duration of 2 ms (90 mT/m) ensured complete dephasing of the water signal.

Implementation of MEGA water suppression in STEAM, as illustrated in Fig. 2A was achieved on a 4 T horizontal (125 cm boresize) whole body imaging system (Siemens, Erlangen, Germany/Varian, Palo Alto, CA), with a 33 cm head gradient insert and a quadrature surface coil.[19] FASTMAP[20] based on the STEAM sequence was used for shimming. Sinc pulses (duration = 2 ms) were used for slice selection, and a 27 mL voxel was localized in the posterior half of the human brain. The carrier frequency of the 180° Gaussian frequency selective pulses (duration = 10 ms) was centered on the water resonance. Trapezoid-shaped gradients (27.5 mT/m, 1.5 ms duration) were used for all water suppression spoilers (G_1–G_3), which were directly programmed into the spectrometer pulse sequence at the time points indicated in Fig. 2, without any further adjustments. The spacing of these gradient pulses was approximately 27 ms and, thus, amounted to a *b* value of less than 3.3 s/mm^2, causing negligible diffusion weighting, since the diffusion constant *D* is typically on the order of 10^{-4} mm^2/s *in vivo*.[21–23] Eddy currents or

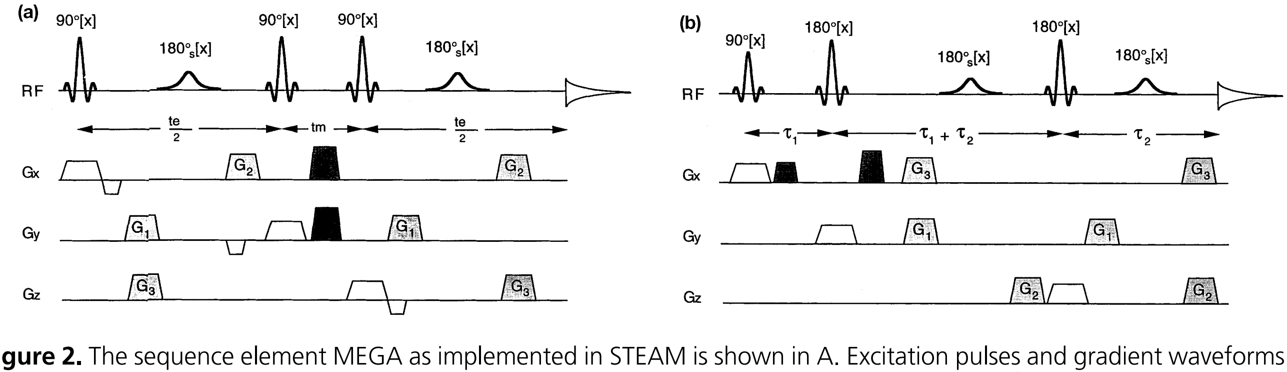

Figure 2. The sequence element MEGA as implemented in STEAM is shown in A. Excitation pulses and gradient waveforms for the PRESS sequence incorporating MEGA are illustrated in B. Gradients G_1, G_2 and G_3 are used for MEGA implementation in both sequences. For suppression of the water signal only, a single-banded frequency selective pulse is used

patient motion did not cause any problems using these specific gradient values and timing, which is consistent with previous experience using DRYSTEAM with $b \sim 54$ s/mm^2.[24] *TM* spoilers (dark shading in Fig. 2A) were 6 ms in duration (27.5 mT/m, *TM* = 10 ms) and *TE* was 34 ms.

To test *in vivo* water suppression and editing performance, MEGA was incorporated into the PRESS and STEAM sequences to acquire human brain *J* difference edited spectra at 4.0 T. For the MEGA–PRESS sequence (Fig. 2B), a 27 mL voxel was localized using a 90° (duration = 2 ms) and two 180° (duration = 3 ms) slice selective sinc pulses. Gradient strengths for water suppression were 22 mT/m (1.5 ms duration). The spacing of these gradient pulses was approximately 54 ms and thus amounted to a b value of less than 4.5 s/mm^2 causing negligible diffusion weighting. In the MEGA-STEAM sequence (Fig. 2A), a 27 mL voxel was also localized using 90° slice selective sinc pulses. Spoiler gradients for the MEGA–STEAM sequence were 27.5 mT/m. Double-banded frequency selective pulses (duration = 20 ms) were used for water suppression and editing in the MEGA–STEAM and MEGA–PRESS sequences. The double-banded pulses were generated from Gaussian pulses as described previously for a clinical system,[25] for which the capability to generate phase-modulated pulses is sufficient. Eight subjects were studied after giving informed consent according to procedures approved by the Institutional Review Board. Subjects were placed supine into a cushioned head holder without any restraints for all studies.

RESULTS AND DISCUSSION

The B_1 insensitivity of MEGA was evaluated by acquiring water spectra from an 18 mm water-filled phantom. The RF power of the frequency selective pulses was varied in 0.5 dB increments using the sequence shown in Fig. 1. Excellent suppression of the water signal was still achieved within 1.5 dB from the optimal setting, which demonstrated the insensitivity of MEGA to flip angle errors (not shown). Assuming a perfect 180° broadband non-selective pulse, and that α_s is the effective flip angle of the selective pulse,[12] the theoretical signal dependence is $\cos^4(\alpha_s/2)$.

To demonstrate the absence of phase distortion, phase sensitive spectra were acquired in which the carrier frequency of these pulses was varied from -1000 to $+1000$ Hz about the water resonance, in 50 Hz increments. As shown in Fig. 3, the phase of the water resonance was constant throughout, demonstrating that water suppression with MEGA avoids signal distortion. On resonance, a suppression factor of 3000 was estimated in a single scan using MEGA.

To demonstrate the usefulness of the method for clinical spectroscopy in the human brain, water-suppressed spectra were acquired in several subjects using the MEGA–STEAM sequence shown in Fig. 2A. A representative spectrum acquired from a voxel in the occipital lobe is presented in Figure 4A (*TE* = 34 ms, *TM* = 10 ms, *TR* = 3 s). Excellent water suppression of at least 3000 was achieved, as judged from the residual water signal, which was smaller than the major ^{1}H metabolite peaks. These results were compared with those obtained using the 3,1-DRYSTEAM sequence (*TE* = 34 ms, *TM* = 33 ms, *TR* = 3 s) implemented as described previously.[24] The residual water signal in the spectrum acquired with 3,1-DRYSTEAM was comparable (Fig. 4B), but exceeds the largest peak of the MEGA spectrum in Fig. 4. Furthermore, 3,1-DRYSTEAM required much longer calibration times for two RF calibrations prior to data acquisition than MEGA, and to achieve that result, *TM* was much longer for 3,1-DRYSTEAM. Although CHESS should, in principle, provide undistorted water line shapes and phases, it is also interesting to note that when using CHESS, the water resonance can have a dispersive line shape and a negative amplitude. Theoretical calculations and experience showed that neither is present for the proposed water-suppression scheme. On the other hand, the minimal achievable *TE* using MEGA for water suppression is longer than that obtained using DRYSTEAM. However, this is not a limitation for the majority of clinical spectroscopy applications in which intermediate and long *TE* times of 135 or 270 ms are used. For example, a 20 ms Gaussian RF pulse results in a suppression bandwidth of 100Hz when used in MEGA, which will not affect chemical shifts below 3.7 ppm. Thus, choline groups (Cho), creatine (Cr), N-acetyl-aspartate (NAA) and lactate can be measured at 1.5 T without intensity distortion, and with only a small reduction in acquisition

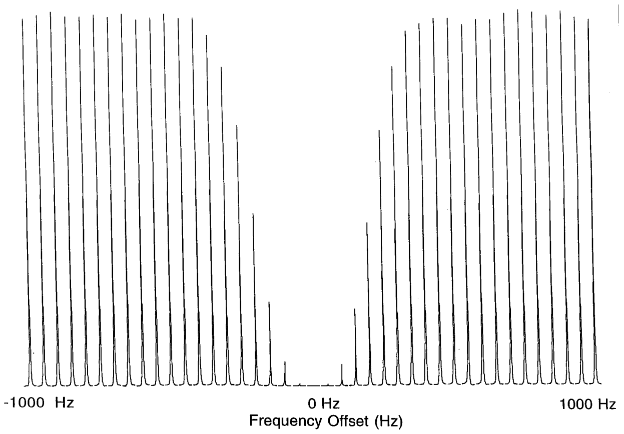

Figure 3. Offset characteristics of MEGA. To demonstrate that phase sensitive spectra do not exhibit phase distortion outside the bandwidth of the frequency selective pulses, the frequency of the selective pulses in MEGA was varied in 50 Hz increments (±1000 Hz) about the water resonance. Spectra were acquired without signal averaging using *TE* = 32 ms and *TR* = 3 s

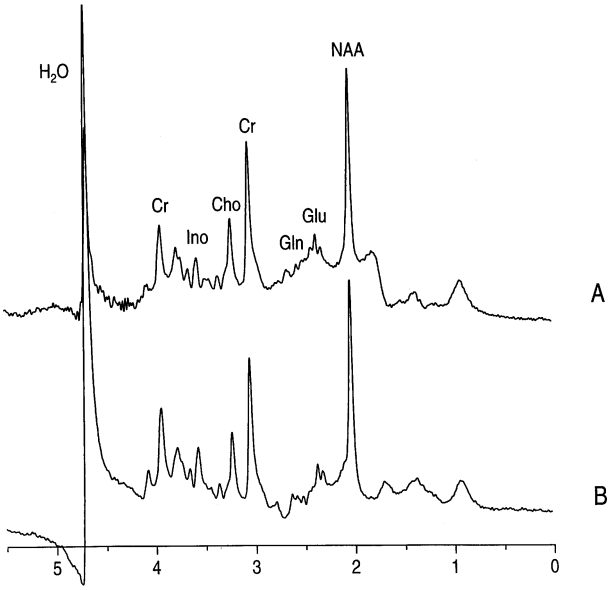

Figure 4. A: Spectrum acquired from a human brain using the MEGA–STEAM sequence shown in Fig. 2A (*TE* = 34 ms, *TM* = 10 ms, *TR* = 3 s, voxel size = 27 mL, NEX = 64, 1 Hz line broadening, total acquisition time = 3.2 min). The carrier frequency of the selective pulses was placed on the water resonance. Note that excellent suppression of the water resonance was achieved without distorting the phase of resonances outside the selective pulse bandwidth. B: For comparison, a 3,1-DRYSTEAM spectrum was acquired from the same subject and location using a *TR* = 3s, *TE* = 34ms and *TM* = 33ms (NEX = 64), and using identical processing. Note that the water peak of this spectrum extends well above the highest peak of the MEGA spectrum shown in A

time when acquiring full echoes. Since the inhomogeneity of the tissue scales with magnetic field, the performance of MEGA at 4 T can be taken as an indication of its expected performance at 1.5 T when implemented in techniques such as chemical shift imaging of larger regions than the 27 mL used here. Relatively short *TE* times are possible with MEGA, as is demonstrated in the water-suppressed spectrum acquired with a *TE* of 34 ms (Fig. 4A).

MEGA can be used to suppress several resonances by applying multi-banded pulses.[25,26] The sequence element MEGA requires that the flip angles for the frequency selective pulses are identical (180°_s) and does not require as careful calibrations as those for CHESS, or variants of CHESS. As a consequence, shorter calibration and scan times may be achieved using MEGA for water suppression. The use of two 180° frequency selective pulses requires twice the RF power of four 90° pulses of the same shape. However, soft water-suppression pulses contribute an insignificant fraction of total power deposition in these sequences.

To illustrate the efficiency of MEGA for simultaneous water suppression and editing, MEGA was incorporated into PRESS, as illustrated in Fig. 2B. We demonstrate editing of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter which may be of critical importance in neurodegenerative diseases such as epilepsy, Huntington's disease, mania and schizophrenia. In the occipital lobe, approximately 1–1.5 mM GABA concentrations have been reported.[27–29] Detection of γ-aminobutyric acid is difficult *in vivo* since the small GABA triplet resonance at 3.02 ppm underlies the intense creatine (Cr) methyl peak at 3.04 ppm,[30] and signals from macromolecules can also be edited.[27,31,32] The GABA triplet resonance at 3.02 ppm can be observed *in vivo*[27–30,33–36] through *J* difference spectral editing.[37]

With the MEGA scheme, spectral editing of GABA was achieved by using double-banded Gaussian 180°_s pulses (duration = 20 ms). With one band set to the resonance frequency of water, the water signal was suppressed as in the standard MEGA scheme. With the second band set to 1.90 ppm (the resonance frequency of the protons coupled to the 3.02 ppm protons), *J* evolution of the outer triplet peaks near 3.02 ppm was refocused. The symmetric counterpart of this pulse, set to the water resonance and 7.54 ppm, suppresses the water resonance, but does not refocus *J* evolution for the GABA resonances at 3.02 ppm. In other words, during odd-numbered acquisitions, the GABA resonance at 1.90 ppm was flipped 180° by the double-banded pulses to refocus *J* evolution at 3.02 ppm. During even-numbered acquisitions, *J* evolution of the GABA resonance at 3.02 ppm was not refocused and thus, the phase of the outer triplet signals was inverted at $TE = 1/J$ (68 ms). Thus, the difference of the acquired spectra provided an edited spectrum of GABA (3.02 ppm), as in similar editing techniques, although water was suppressed simultaneously. The creatine (Cr) methyl resonance was not affected by the frequency selective pulses in either of the two acquisitions. As a consequence, the intense Cr resonance (3.04 ppm), which obscures the γ-CH$_2$ GABA triplet at 3.02 ppm, was eliminated using difference spectroscopy. Complete elimination of resonances not coupled to the region at 1.9 ppm was verified in phantom spectra (not shown). Elimination of spin systems not having a coupling partner at approximately 1.9 ppm can also be verified *in vivo* from the complete elimination of *myo*-inositol, Cho and NAA aspartyl resonances at 2.7 ppm and the creatine methylene peak at 3.93 ppm.

A *J* difference edited spectrum of GABA, acquired from a voxel in the human visual cortex using the MEGA–PRESS sequence (Fig. 2B), is shown in Fig. 5. The creatine resonance at 3.04 ppm was eliminated using difference spectroscopy. Tentatively, the resonance at 3.02 ppm was assigned to the γ-CH$_2$ GABA triplet, since (1) the measured *in vivo* linewidth of 22 Hz is in excellent agreement with that measured in a phantom spectrum (21 Hz), which was line broadened such that the Gly linewidth matched that of creatine *in vivo*; (2) the chemical shift of this resonance (3.02 ppm) coincides with that measured in the phantom; and (3) residual signal contributions of creatine to the peak at 3.02 ppm

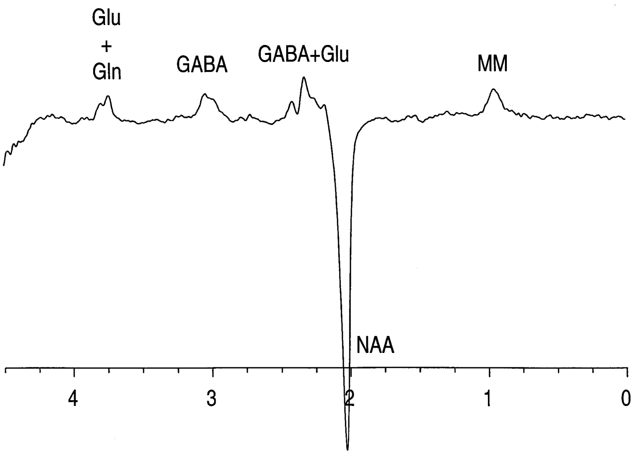

Figure 5. An edited spectrum from a voxel in the occipital area of a human subject acquired using MEGA–PRESS (Fig. 2B). Parameters for the displayed spectrum are : *TE* = 68 ms, *TR* = 3 s, voxel size = 27 mL, NEX = 64, total acquisition time = 6.4 min

caused because of subtraction errors *in vivo*, were considered unlikely, since the latter had a linewidth of 21 Hz, which was at least 14 Hz broader than that typically measured for creatine. The negative NAA peak in Fig. 5 occurs because of the finite bandwidth of the 20 ms Gaussian pulses applied at 1.90 ppm, which causes some reduction in NAA signal in one of the subspectra. The glutamate H4 at 2.37 ppm, and the H2 intensity at 3.76 ppm, were attributed to partial editing because the same effect occurred for the frequency selective pulses on the glutamate H3 coupling partner at 2.1 ppm.

Unfortunately, a nearby macromolecule (MM) resonance at 1.7 ppm may also coedit its '*J*-partner' at approximately 3.0 ppm,[27] despite the use of narrow band frequency pulses to selectively excite the β-CH_2 GABA resonance at 1.90 ppm. To ascertain whether excitation of the MM resonance at 1.7 ppm caused significant co-editing of the MM resonance, which overlaps with the γ-CH_2 GABA triplet at 3.02 ppm, several spectra were acquired using the MEGA–STEAM sequence (Fig. 2A), using the same double-banded pulses (20 ms duration) placed on the water resonance and 476 Hz on either side of the water resonance as above. To determine if the MM peak contributes to the GABA resonance at 3.02 ppm, an inversion pulse was applied prior to the MEGA–STEAM sequence. Since MM have a substantially shorter T_1 than metabolites at 2.1 T[38] as well as at 4 T (unpublished results), the inversion time was adjusted to minimize the creatine resonance. Since the T_1 values of metabolites are typically comparable, the GABA resonance becomes minimal as the creatine and NAA signals are minimized. With an inversion pulse designed to null the creatine resonance applied prior to MEGA–STEAM, mostly resonances with shorter T_1 than that of creatine and NAA (i.e. macromolecules and lipids) were evident in the spectra.

The results of these experiments are illustrated in Fig. 6. The GABA edited spectrum in Fig. 6A, acquired using MEGA–STEAM (Fig. 2A), shows the GABA resonance at 3.02 ppm and glutamate resonances between 2.1 and

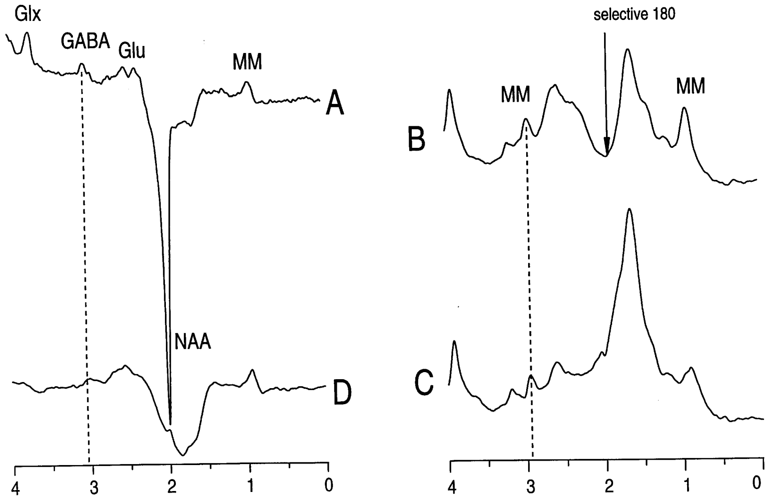

Figure 6. A series of *in vivo* spectra acquired using the MEGA–STEAM sequence shown in Fig. 2A. Parameters for the displayed spectrum include: *TE* = 68 ms, *TM* = 15 ms, *TR* = 3 s, voxel size = 27 mL, total acquisition time = 6 min for B and C, and 13 min for A and D. The GABA edited spectrum is shown in A. To demonstrate that the peak at 3.02 ppm is primarily attributable to the GABA triplet, a pre-inversion pulse was applied in order to null the metabolite signals (in B and C). In B (with pre-inversion) the double-banded frequency selective pulse is applied at the water resonance and at 1.90 ppm. In C (with pre-inversion), the double-banded pulse is placed on the water resonance and 7.54 ppm. The macromolecule resonance is visible at 2.98 ppm in B and C. The difference spectrum of B and C is shown in D. The metabolites are nulled and the resonance at 3.02 ppm is well suppressed

2.4 ppm. In Fig. 6B, an inversion pulse that minimized the creatine resonance was placed prior to the otherwise identical MEGA–STEAM sequence. The pre-inversion pulse was also applied to acquire the spectrum shown in Fig. 6C, but the double-banded pulse was set to the water resonance and 7.54 ppm. The excellent quality of inversion can be judged from the NAA null. In Fig. 6B and C, a MM resonance is clearly observable at 2.98 ppm, which was distinct from the GABA position at 3.02 ppm. The difference between the spectra in Fig. 6B and C, is illustrated in Fig. 6D. The metabolites are nulled (note the minimization of the NAA peak, and almost complete suppression of the resonance at 3.02 ppm), which suggests improved editing because of increased spectral resolution at 4.0 T. The almost complete null of the tentative GABA peak at 3.02 ppm, its adequate line-width, and the distinct chemical shift of the pertinent MM resonance (2.98 ppm), support the assignment of the resonance at 3.02 ppm to GABA.

Preliminary GABA concentrations estimated in four subjects, using the MEGA–STEAM and MEGA–PRESS sequences, were $\sim$1.2 mM relative to 10 mM Cr assuming identical T_1 and T_2 values. This value is in excellent agreement with previously reported results,[27,28,29] which further supports the validity and efficiency of the proposed editing method. Water suppression and editing was reproducible and comparable with that shown in Figs 4,5,6. All GABA intensity estimations were between 0.8 and 1.4 μmol/g.

In conclusion, excellent water suppression can be achieved with MEGA without distorting the phase of the peaks of interest. It is also robust with respect to B_1 field inhomogeneities and T_1 relaxation. These properties of MEGA may be advantageous for selective suppression in many sequences, including chemical shift imaging,[39,40] at intermediate and long echo times. The method can also be used to edit coupled spin systems in minimal sequence time when using multi-band suppression pulses, as demonstrated for the spin system of GABA in the human brain.

Acknowledgements

This work was supported by NIH Grants RR08079 and CA64338. We also thank Melissa Terpstra and Dr Wolfgang Richter for helpful suggestions on the manuscript.

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