Comparison of T_1 Relaxation Times of the Neurochemical Profile in Rat Brain at 9.4 Tesla and 14.1 Tesla

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Knowledge of T_1 relaxation times can be important for accurate relative and absolute quantification of brain metabolites, for sensitivity optimizations, for characterizing molecular dynamics, and for studying changes induced by various pathological conditions. ^{1}H T_1 relaxation times of a series of brain metabolites, including J-coupled ones, were determined using a progressive saturation (PS) technique that was validated with an adiabatic inversion-recovery (IR) method. The ^{1}H T_1 relaxation times of 16 functional groups of the neurochemical profile were measured at 14.1T and 9.4T. Overall, the T_1 relaxation times found at 14.1T were, within the experimental error, identical to those at 9.4T. The T_1s of some coupled spin resonances of the neurochemical profile were measured for the first time (e.g., those of γ-aminobutyrate [GABA], aspartate [Asp], alanine [Ala], phosphoethanolamine [PE], glutathione [GSH], N-acetylaspartylglutamate [NAAG], and glutamine [Gln]). Our results suggest that T_1 does not increase substantially beyond 9.4T. Furthermore, the similarity of T_1 among the metabolites (~1.5 s) suggests that T_1 relaxation time corrections for metabolite quantification are likely to be similar when using rapid pulsing conditions. We therefore conclude that the putative T_1 increase of metabolites has a minimal impact on sensitivity when increasing B_0 beyond 9.4T. Magn Reson Med 62:862–867, 2009.

Key words: proton magnetic resonance spectroscopy; T_1 relaxation times; neurochemical profile; rat brain; high magnetic field

Very high magnetic field strengths (>7T) are currently available for in vivo studies on humans and animals. Studies at these very high magnetic fields benefit from higher signal-to-noise ratio (SNR) and increased spectral dispersion. Consequently, proton magnetic resonance spectroscopy (MRS) became an important tool for noninvasively investigating brain metabolism. At these magnetic fields, knowledge of T_1 relaxation times is important for accurate relative and absolute quantification of brain metabolites when the repetition time is on the order of T_1, such as in quantitative spectroscopic imaging, for optimizing measurement protocols, for characterizing molecular dynamics, and for studying concentration changes induced by various pathological conditions (1–3).

T_1 relaxation times have been measured at 9.4T and 11.7T (1) for a few proton resonances, and a general trend toward increased T_1 has been observed with increasing B_0. This study and others (2,4–9) have focused on the estimation of the T_1 relaxation times of a few brain metabolites, mainly the singlets such as total choline, total creatine (tCr), *N*-acetylaspartate(NAA)+N-acetylaspartylglutamate (NAAG), and in a very few cases the T_1s of specific coupled multiplets (inositol at 3.57 ppm or glutamate-(Glu)+glutamine (Gln) at 2.35 ppm). The quantification of in vivo short echo-time ^{1}H MRS spectra is difficult because of overlaps between metabolite and macromolecule signals. Therefore, previous studies have mainly been performed at long TE values to minimize the contribution of macromolecule signals. At this long TE value, however, the J-coupled spectral multiplets are generally distorted, thus making their quantification and the subsequent T_1 estimation difficult.

The most common techniques for measuring the T_1 relaxation times of brain metabolites are inversion-recovery (IR) (10) and progressive saturation (PS) (11). A drawback of the IR method, compared to the PS technique, is the superposition of spectral lines with opposite signs due to the different T_1 of the metabolites, which may provide a complicated spectral pattern. Thus, using the IR technique, primarily the T_1 relaxation times of singlets or of specific coupled multiplets (e.g., inositol at 3.57 or 3.65 ppm or Glu + Gln at 2.35 or 3.75 ppm) were estimated.

With the availability of the first 14.1T/26-cm MR system, we recently implemented and assessed the performance of ultrashort echo-time proton localized spectroscopy of rat brain in vivo and demonstrated new spectral features at 14.1T (12) not seen previously at 9.4–11.7T.

Therefore, the goal of this study was to measure T_1 relaxation times of proton signals, both singlets and J-coupled multiplets, of rat brain metabolites and to determine whether T_1 of the neurochemical profile further increases at 14.1T. For this reason we calculated T_1 relaxation times of 16 components of the neurochemical profile at 9.4T and 14.1T in rat brain in vivo under identical conditions using a PS technique (e.g., by varying TR) that was validated with an adiabatic IR measurement for selected metabolites.

METHODS

Animals

All animal experiments were conducted according to federal and local ethical guidelines and protocols were approved by the local regulatory body. In vivo experiments were performed on adult female Sprague-Dawley rats (six

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animals at each magnetic field; ~250 g) that were anesthetized during the experiments with 1.5% to 2.5% isoflurane using a nose mask. Body temperature was maintained at 37.5 ± 1.0°C by circulating warm water around the animals.

MRS Measurements

All data were acquired under identical conditions using two MR instruments from Varian (Palo Alto, CA, USA): an INOVA spectrometer interfaced to a 9.4T, actively-shielded magnet with a 31-cm horizontal bore, and an MRI System interfaced to a 14.1T magnet with a 26-cm horizontal bore (both magnets from Magnex Scientific, Oxford, UK). The magnets were equipped with 12-cm inner-diameter actively-shielded gradient sets with a maximum gradient of 400 mT/m in 120 μs. Home-built 14-mm-diameter ^{1}H quadrature surface coils were used as transceivers. Eddy currents were minimized using time-dependent quantitative eddy-current field mapping (13). The static field homogeneity was adjusted using first- and second-order shims using an echo planar imaging (EPI) version of FASTMAP (14). Localizer images were obtained in the coronal planes using a multislice fast spin echo protocol with TE/TR = 60 ms/5000 ms, slice thickness = 1 mm, and in plane resolution = 94 μm. Spectra were obtained by an ultrashort echo time (TE/TR = 2.8 ms/4000 ms, complex data points = 4096, SW = 7 kHz, 320 averages at 9.4T and 160 averages at 14.1T) spin-echo full-intensity acquired localization (SPECIAL) technique (12,15). The size of the voxel for ^{1}H MRS was 3 × 4 × 5 mm^3 including frontal cortex, corpus callosum, and striatum. The reproducibility of the voxel placement was based on anatomical landmarks. The voxel was positioned 0.3 mm posterior to bregma and 3.4 mm ventral. Identical radio frequency (RF) pulses, gradient amplitudes, and sequence timing were used on both instruments. After first- and second-order shimming, the typical linewidth of water resonance at TE = 2.8 ms was 12–14 Hz at 9.4T and 18–20 Hz at 14.1T. Water signal was suppressed by a series of seven 25-ms asymmetric variable-power RF pulses with optimized relaxation delays (VAPOR) (16). The water-suppression pulses were interleaved with three modules of outer volume saturation, as described elsewhere (16). To compensate for the magnetic field drift, spectra were collected in blocks of 16 averages that were stored separately in the memory and were corrected for the relative shift in frequency.

T_1 measurements were accomplished using a PS technique (by changing TR in the range from 1 s to 10 s, nine measurements, TE = 2.8 ms) that was validated with an adiabatic IR experiment for selected resonances. For the IR measurements, the SPECIAL sequence was extended with a 2-ms nonselective adiabatic inversion pulse (a bandwidth = 10 kHz), which was applied before starting the localization part of the sequence. TI was varied in the range from 0.1 to 1.8 s and a fully-relaxed spectrum was obtained to determine equilibrium magnetization values at TE = 20 ms for selected metabolites. To eliminate the effect of partial saturation, the spectra with different TIs were collected with the same relaxation delay. The TE was chosen to be 20 ms in order to partially eliminate the contribution of macromolecule resonances, thus making the quantification of the IR time series more accurate.

Data Analysis

The PS series were analyzed using LCModel (17), combined with a simulated basis-set of metabolites containing the spectrum of macromolecules measured in vivo as described previously (6,12). Other than the experimentally measured macromolecule spectrum, the basis set at both magnetic fields was created by quantum mechanics simulations, based on the density-matrix formalism (18), using published values of J-coupling constants and chemical shifts (19). To obtain individual T_1s of different groups in the same molecule, the basis sets contained separate spectra of acetyl and aspartyl moieties of NAA, and signals of the CH_3 and CH_2 groups of tCr. The Cramér-Rao lower bounds (CRLBs) were calculated by LCModel as a measure of the reliability of the metabolite estimates. The T_1 relaxation times were estimated for the following functional 16 groups of metabolites: tCr at 3.03 ppm (Cr+PCr), the methylene resonances of tCr (Cr+PCr*), the NAA acetyl moiety (NAA), the aspartyl resonance of NAA (NAA*), taurine (Tau), total choline (Cho), Glu, Gln, myoinositol (Ins), alanine (Ala), aspartate (Asp), γ-aminobutyrate (GABA), glutathione (GSH), NAAG, phosphoethanolamine (PE), and macromolecules (Mac). The T_1 for Glc and Lac were not estimated due to their dependence on animal physiology, such as anesthesia and glycemia.

The IR measurement was evaluated using the jMrui software (available online at http://www.mrui.uab.es/mrui). No water removal was performed as a preprocessing step. The signals were fitted using the "advanced method for accurate, robust, and efficient spectral" fitting (AMARES) (20). For quantification purposes, the in vivo data were Lorentzian line broadened with 20 Hz. For each in vivo signal of the time-series, 13 Lorentzian spectral components were selected to fit the major contributions of the metabolites, the zero-order phase was estimated and the first-order phase was fixed to zero. The individual phases relative to the zero-order phase were fixed to zero or to 180° depending on the inversion time. Linewidths were constrained to a predetermined interval. To minimize the influence of the large broad baseline components linked to the macromolecule resonances, the first 20 data points of the in vivo signals were weighted with a quarter-sine wave. Thus the T_1 relaxation times of macromolecules were not reliably estimated. The accuracy of the amplitude estimates was assessed using the CRLBs (21). The T_1 relaxation times were estimated for the following spectral lines: the singlet of *N*-acetylaspartate and NAAG at 2.01 ppm [NAA]; two lines of a triplet of glutamate at 2.35 ppm [Glu(2.35)]; singlets of tCr at 3.03 ppm [Cr+PCr] and choline-containing compounds at 3.22 ppm [Cho]; the triplet of Tau at 3.42 ppm (Tau); spectral lines of myoinositol at 3.57 ppm [Ins(3.57)], 3.65 ppm [Ins(3.65)], and 4.05 ppm [Ins(4.05)]; a broader signal of Gln and Glu at 3.75 ppm [Glx (3.75)]; and a singlet of tCr at 3.92 ppm [Cr+PCr*].

The T_1 relaxation curves were fitted with nonweighted two-parameter single-exponential functions based on a Levenberg-Marquardt algorithm, fitting the M(0) and T_1 for

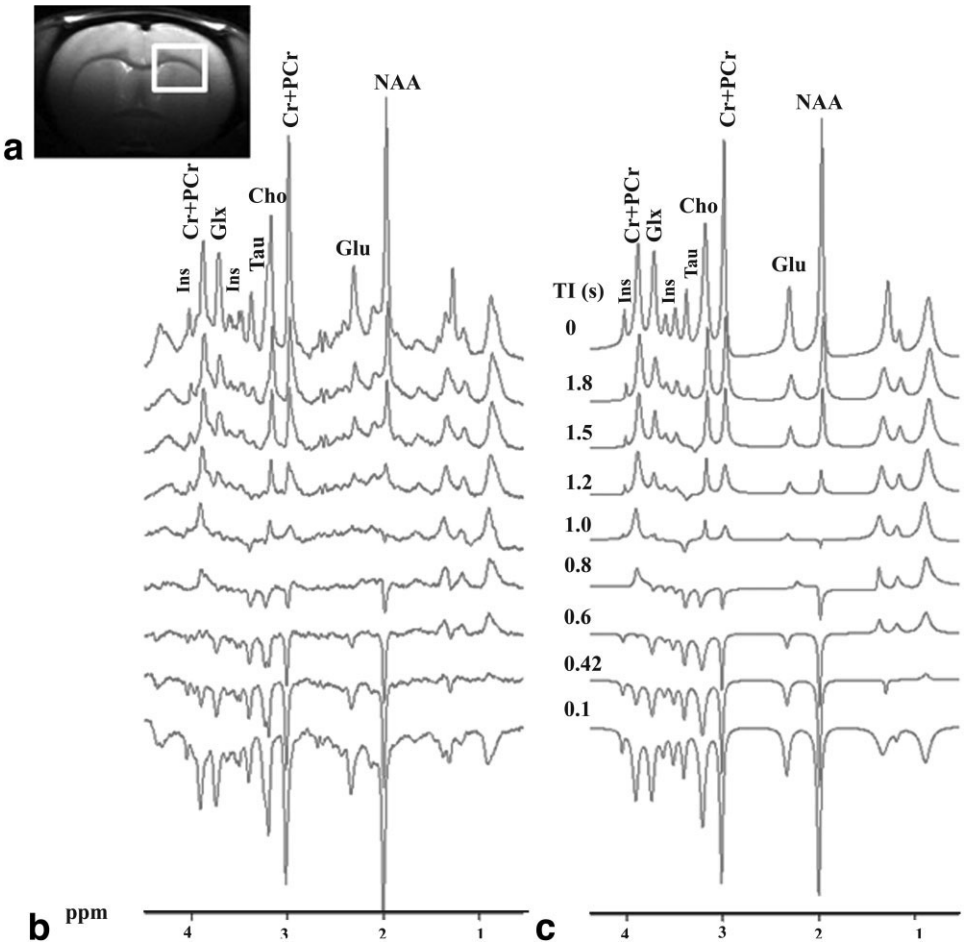

FIG. 1. **a:** Coronal view of a rat brain showing a typical position of a volume of interest. One series of in vivo spectra acquired at 14.1T in the rat brain with different inversion times (TI), ranging from 0 to 1.8 s, and TE = 20 ms (**b**) and the corresponding estimates using AMARES (**c**). For quantification purpose the in vivo data were Lorentzian line-broadened with 20 Hz. No preprocessing for water signal removal was applied.

the IR series and equilibrium magnetization and T_1 for the PS series. For each fit, the correlation coefficients reflecting the quality of the least squares fit vs. the original data were computed. A typical standard error of the fitted T_1 was about 5%.

To evaluate any possible increase of T_1 at 14.1T, the differences between the mean T_1 relaxation time estimates at 14.1T and 9.4T and the corresponding standard errors (with *P*-values) were computed for each metabolite. In addition, the T_1 estimates obtained at both magnetic fields were statistically compared using an unpaired two-tailed Student's *t*-test.

RESULTS

In general, spectra exhibited excellent SNR (Fig. 1) using the IR approach. Notable differences in T_1, such as of Cr+PCr*, Tau, NAA, and Mac, were discernable with varying TI. As can be seen in Fig. 1, the shorter times of zero crossing were ~0.42 s for Mac and ~ 0.6 s for Cr+PCr*, whereas NAA and Tau had longer zero-crossing times, ~1 s and ~1.2 s, respectively. The T_1 relaxation times (mean ± SD) of 10 components of the neurochemical profile obtained using the IR technique at 9.4T and 14.1T, are shown in Fig. 2. The measured amplitudes of the 10 selected metabolites showed excellent agreement with the best fits (Fig. 1). The corresponding CRLBs of the amplitude estimates were below 20% for all 10 evaluated compounds. The T_1 were in a relatively narrow range from 1.2 s to 1.5 s for all metabolites. The notable exceptions were Tau (~2.2 s at both magnetic fields) and the methylene resonance of Cr+PCr (~1 s at both magnetic fields). The SDs of the T_1 relaxation times calculated from six animals were between 2% and 10% for most metabolites. The correlation coefficients reflecting the quality of the least squares fit vs. the original data were between 0.91 and 0.99. Using the IR method, the T_1 measured at 14.1T were, within the experimental error, identical to those measured at 9.4T for most metabolites (Fig. 2). NAA was the only metabolite that showed a statistically significant increase ($P = 0.004$) with increasing B_0. The difference between the mean T_1 estimates at 14.1T and 9.4T was only 8% (with $P = 0.001$) for NAA, whereas for the other metabolites this difference was between 0.0 and 0.09 s and it was not statistically significant.

As with the IR technique, spectra acquired using the PS technique exhibited excellent SNR (Fig. 3). Differences in T_1 between metabolites were also discernible in these series of spectra. As can be seen in Fig. 3, the amplitudes of NAA, Cho, Cr+PCr, and particularly Tau dropped down substantially at TR = 1 s compared with TR = 4 s, whereas the decrease of amplitudes of Cr+PCr* and NAA* was relatively small and there was no change in the amplitude

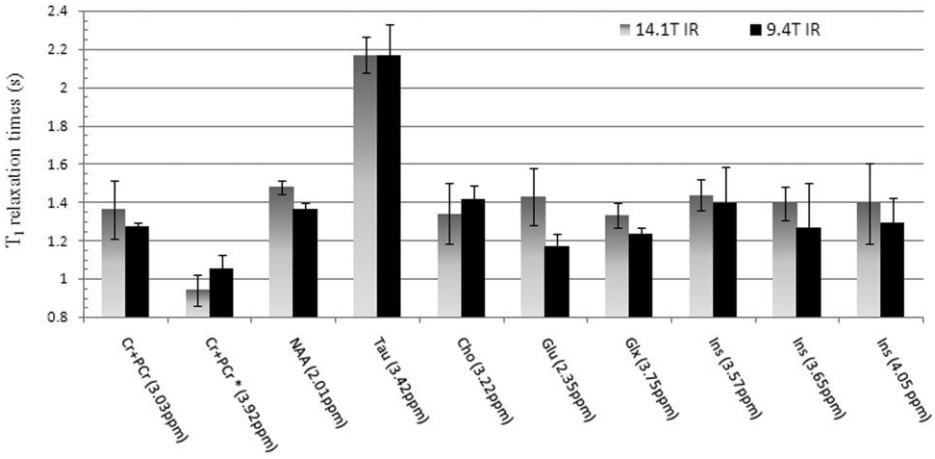

FIG. 2. T_1 relaxation times (mean ± SD) of 10 resonances of the neurochemical profile estimated at 14.1T (light bars) and 9.4T (black bars) in the rat brain using the IR technique. *Methylene resonance.

of the Mac signals in the range of 0.9 ppm to 1.8 ppm. When using the progressive saturation technique in combination with LCModel (Fig. 3), the high spectral resolution and sensitivity allowed the estimation of T_1s for 16 metabolites or their specific functional groups, as demonstrated by the good agreement between the in vivo data and the best fits. The precision of the metabolite quantification was assessed using the CRLBs obtained from the LCModel analysis. The CRLBs of singlets and coupled resonances of highly concentrated metabolites such as Cr, NAA, Glu, Ins, and Tau were below 5% at 9.4T and 14.1T. For metabolites such as Gln, GABA, Ala, Asp, NAAG, PE, GSH, which are present at lower concentration and also suffer from large overlap with other resonances, the CRLBs were below 20% at both magnetic fields. Overall, the high spectral resolution and SNR afforded at both magnetic fields allowed the estimation of the T_1 for the 16 components of the neurochemical profile which had CRLBs < 20%. At both magnetic fields, the T_1 relaxation times were found in a relatively narrow range from 1.4 s to 1.9 s for all metabolites, except for Tau (~2.6 s at both magnetic fields) (Fig. 4). The aspartyl resonance of NAA (NAA*) and methylene resonance of Cr+PCr had shorter T_1 (~1.2 s for NAA* and ~1.1 s for Cr+PCr* at both magnetic fields) than the corresponding methyl resonances. As in previous studies, the macromolecules had a markedly shorter T_1 (0.66 ± 0.07 s at 14.1T and 0.51 ± 0.07 s at 9.4T). The SDs of the T_1 estimates were between 1% and 10% for most metabolites. Figure 5 displays examples of the monoexponential fittings of the in vivo Gln, NAA, NAA*, Tau, Asp amplitude evolutions at 14.1T and 9.4T, respectively. The correlation coefficients were between 0.91 and 0.99 at both magnetic fields. Overall, the T_1 measured at 14.1T were within the experimental error the same as those at 9.4T (Fig. 4). NAA and Mac were the only metabolites that showed a statistically significant increase ($P = 0.001$ for NAA and $P = 0.007$ for Mac). Like for the IR technique, the difference between the mean T_1 estimates at 14.1T and 9.4T was only 11% (with $P = 0.001$) for NAA, whereas for the other metabolites the difference was between 0.01 s and 0.06 s and was not statistically significant.

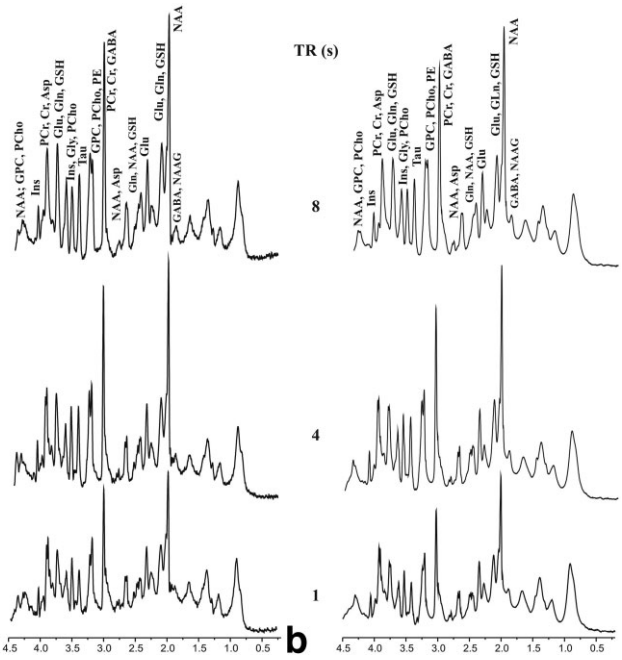

FIG. 3. One series of in vivo spectra acquired at 14.1T in the rat brain with different repetition times (TR) and TE = 2.8 ms (**a**) and the corresponding estimates using LCModel (**b**). A shifted Gaussian function $\exp[-(t - 0.04)^2/0.08^2]$ was used for modest resolution enhancement. No baseline correction or preprocessing for water signal removal was applied.

The T_1 relaxation times obtained with the two methods were the same within ~15% (Figs. 2 and 4). At both magnetic fields, the T_1 values of some metabolites (Cr+PCr, Cr+PCr*, NAA, and Tau) obtained by the PS technique appeared to be slightly higher ($P = 0.001$) compared to those measured by the IR technique.

DISCUSSION

This study reports in vivo T_1 relaxation times of singlets as well as coupled spin resonances of 16 cerebral metabolites at 9.4T and 14.1T, including for the first time the T_1s of GABA, Asp, Ala, PE, GSH, NAAG, and Gln. The high spectral resolution and sensitivity allowed the estimation of ^{1}H T_1s of 16 metabolites using the progressive saturation

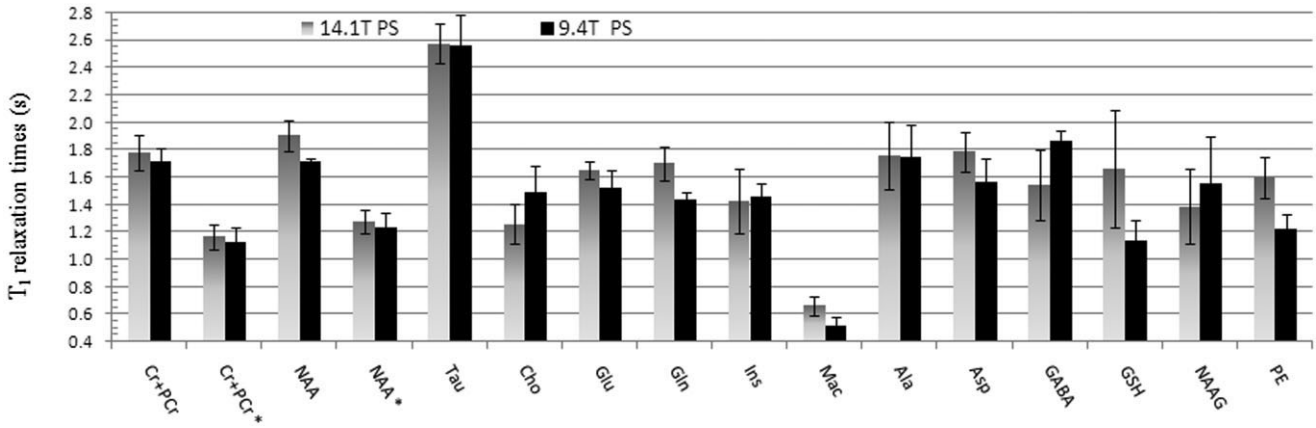

FIG. 4. T_1 relaxation times (mean ± SD) of 16 components of the neurochemical profile estimated at 14.1T (light bars) and 9.4T (black bars) in the rat brain using the progressive saturation technique and LCModel analysis of the indicated spin systems. *Methylene and aspartyl resonances.

approach, that were in excellent agreement with those obtained by IR for selected metabolites.

The IR spectra with intermediate TIs exhibit a superposition of spectral lines with opposite phases due to the different T_1 of the metabolites, which provides a very complicated spectral pattern. Thus the IR spectra were difficult to analyze by LCModel. We therefore used AMARES for the quantification of selected IR time series signals. The amplitudes of the 10 selected metabolites were successfully estimated using AMARES for all the time series of signals as demonstrated by the excellent agreement between the in vivo data and the estimated data (Fig. 1c). The T_1s of specific coupled multiplets (glutamate at 2.35 ppm; taurine at 3.42 ppm; spectral lines of myoinositol at 3.57 ppm, 3.65 ppm, and 4.05 ppm; and Gln and glutamate at 3.75 ppm) are estimated and are not the T_1s of the whole metabolites as in the PS spectra. The SDs of the T_1 estimates using the IR technique were not significantly different for the two magnetic fields.

As with the IR technique, the SDs of the T_1 relaxation times calculated from six animals using the progressive saturation approach were not significantly different for the two magnetic fields. However, a slight decrease of the SDs was noticed at 14.1T despite the number of averages at 9.4T being two times higher than at 14.1T.

Our results showed a slight increase in the T_1 relaxation times using the PS technique compared with the IR one. It is well known that the accuracy of the relaxation time estimates also depends on the accuracy of the quantification of the spectral lines. Thus, it is very likely that the differences between the T_1s obtained with the two approaches are probably due to the different algorithms used to quantify the metabolites. The two software packages used in this study present their own characteristics (17,20,22). Briefly, in LCModel the metabolite basis set represents the prior knowledge, whereas in AMARES the prior knowledge is introduced by the user. Additionally, the two quantification methods handled the macromolecule contributions differently. For LCModel an in vivo measured macromolecule spectrum was used, whereas for AMARES the first data points of the in vivo signals were weighted. Another possible explanation of the differences between the T_1 relaxation times obtained with the two techniques can be related to imperfect pulse flip angles. Indeed, the IR technique is less sensitive to pulse imperfections and the adiabatic hyperbolic secant RF pulse

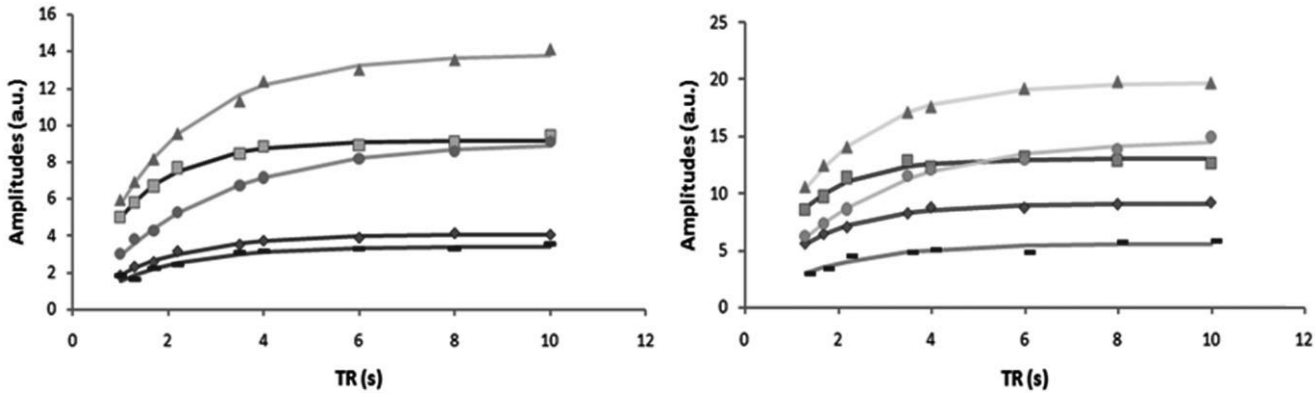

FIG. 5. Monoexponential fitting (line) of the in vivo amplitude evolutions of Gln (◇), NAA (△), NAA* (□), Tau (○), Asp (–) at 14.1T (left part) and 9.4T (right part) in the rat brain for the T_1 estimations using the progressive saturation technique. The estimated amplitudes (dots) are drawn as a function of the repetition times (TR). For the presented fits the correlation coefficients were between 0.96 and 0.99.

added prior to the SPECIAL sequence gives a perfect inversion. The PS technique combined with the surface coils is sensitive to the imperfect flip angle setting, causing a systematic bias of the calculated T_1 relaxation times (11). Simulations show that the calibration using slice-selective RF pulses based on the maximum amplitude of the acquired signal provides slightly overestimated RF pulse flip angles, which in turn leads to longer calculated T_1 values.

Nevertheless, the T_1 relaxation times obtained using the IR method were the same within ~15% of those obtained using the PS techniques. Such a consistency can be taken as a validation. For quantification, where TR $\geq T_1$, such small variations in T_1 are unlikely to have a substantial impact on the derived concentrations.

The T_1s obtained at 9.4T are very close to those obtained for a small number of metabolites in previous studies at 9.4T and 11.7T in rats (1,6). At both magnetic fields, the T_1s were found in a relatively narrow range except for Tau. The T_1 values of NAA, Cr+PCr, and Cho obtained at 9.4T using the IR method were in agreement with previous IR studies at 9.4T (6). In particular, the high T_1 of Tau was consistent with another study (1). Interestingly, the aspartyl resonance of NAA (NAA*) had shorter T_1 than the corresponding methyl resonances. Likewise, the T_1 of the methylene resonance of Cr+PCr (Cr+PCr*) in our study was shorter and in agreement with previous works (1,2,6,7).

A previous study (1) reported the T_1 relaxation times of seven components of brain metabolites plus the macromolecules at 4.7T, 9.4T, and 11.7T. Taking these seven components from our T_1 relaxation times of 16 components of the neurochemical profile obtained at 9.4T and 14.1T we noted good agreement with the values reported in that study at 11.7T, suggesting that T_1s do not increase substantially beyond 9.4T. For example, the T_1 of Mac measured in our study was 0.66 ± 0.07 s, whereas the T_1 reported at 11.7T was between 0.62 s and 0.76 s. For most other metabolites, the T_1s obtained in our study were, within the experimental errors, in agreement with the values reported at 11.7T (1). It is interesting to note that Cho had a slightly shorter T_1 (~20%) in our study at 14.1T than the T_1 reported at 11.7T in Ref. 1. This difference might be due to a complicated way of quantifying the signal intensity of Cho in Ref. 1. However, while this previous study suggested that T_1 increases with B_0, T_1s at 14.1T were identical, within experimental errors, to those at 9.4T (Figs. 2 and 4). Therefore, the relative narrow range of T_1s estimated in our study at both magnetic fields, combined with the lack of a substantial increase at 14.1T, indicate that at 14.1T the T_1 relaxation time corrections for metabolite quantification routines are likely to be similar when using rapid pulsing conditions and some differential corrections may be necessary for Tau and Cr+PCr*. According to the Ernst angle (23), if TR ≈ 2 s is used (in spectroscopic imaging), providing the maximum SNR in a given measurement time, the loss in sensitivity for Tau will then be ~23%.

In summary, we measured for the first time the T_1 relaxation times of 16 components of the neurochemical profile using the PS method combined with LCModel. The obtained T_1 relaxation times at 14.1T were identical, within the experimental error, to those at 9.4T. In addition, our T_1 values are in good agreement with the published data at 9.4T and 11.7T and suggest that T_1s do not increase substantially beyond 9.4T. We therefore conclude that the putative T_1 increase of metabolites has a minimal impact on sensitivity when increasing B_0 beyond 9.4T.

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