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MR imaging of high-grade brain tumors using endogenous protein and peptide-based contrast

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ABSTRACT

Amide proton transfer (APT) imaging is a novel MRI technique, in which the amide protons of endogenous proteins and peptides are irradiated to accomplish indirect detection using the bulk water signal. In this paper, the APT approach was added to a standard brain MRI protocol at 3 T, and twelve patients with high-grade gliomas confirmed by histopathology were scanned. It is shown that all tumors, including one with minor gadolinium enhancement, showed heterogeneous hyperintensity on the APT images. The average APT signal intensities of the viable tumor cores were significantly higher than those of peritumoral edema and normal-appearing white matter ($P<0.001$). The average APT signal intensities were significantly lower in the necrotic regions than in the viable tumor cores ($P=0.004$). The APT signal intensities of the cystic cavities were similar to those of the viable tumor cores ($P>0.2$). The initial results show that APT imaging at the protein and peptide level may enhance non-invasive identification of tissue heterogeneity in high-grade brain tumors.

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Introduction

High-grade gliomas in patients are invasive and histologically heterogeneous. These brain tumors typically consist of a solid tumor mass, often mixed with necrosis, and individual tumor cells infiltrating into edematous or even normal-appearing brain tissue (Burger et al., 1983; Kelly et al., 1987). Currently, these tumors are generally evaluated using gadolinium contrast-enhanced MRI, in combination with T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI, which are used to determine the extent of involvement, to guide treatments, and to assess a therapeutic response (Chang et al., 2009). However, existing MRI techniques are not sufficiently tissue-specific and suffer from several limitations. First, gadolinium enhancement on the post-contrast T1-weighted images reveals focal areas of tumor where the blood–brain barrier is disrupted, but it does not show large areas of infiltrating tumor (Kelly et al., 1987). Another limitation is that some high-grade gliomas demonstrate no gadolinium enhancement (Scott et al., 2002; Segall et al., 1990). In this case, it can be difficult to identify the most malignant portions of tumor prior to surgery or local therapies. Third, gadolinium enhancement is not always specific for tumor grade, as low-grade gliomas occasionally enhance (Knopp et al., 1999). Fourth, gadolinium enhancement occurs in any area of a blood–brain barrier disruption, such as treatment-related injury (Brandsma et al., 2008; Mullins et al., 2005), regardless of etiology. Finally, glioma patients require frequent MRI exams and gadolinium exposure has risk in patients with renal insufficiency (Broome, 2008). These imaging limitations have immediate clinical repercussions that may make diagnosis problematic and render local therapies ineffectual. In recent years, there has been much progress in tumor assessment using more advanced MRI approaches, including MR spectroscopy (Graves et al., 2001; Vigneron et al., 2001), diffusion imaging (Field and Alexander, 2004; Lu et al., 2004; Price et al., 2003; Sinha et al., 2002), perfusion imaging (Cha, 2004; Covarrubias et al., 2004), or a combination of these techniques (Catalaa et al., 2006; Law et al., 2003; Verma et al., 2008). Despite these, additional MR approaches, especially tissue-specific ones that use endogenous contrast agents, are much needed.

Amide proton transfer (APT) imaging is a new MRI technique that detects endogenous, low-concentration mobile proteins and peptides in tissue using a change in bulk water intensity due to saturation transfer of the amide protons in the peptide bonds (Zhou et al., 2003a,b). This technique, without the need for exogenous contrast agents, is based on the recently emerged chemical exchange saturation transfer (CEST) sensitivity enhancement approach (Aime et al., 2002; Ward et al., 2000;

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Zhang et al., 2001; Zhou and van Zijl, 2006). When applied to imaging of human brain tumors, the pilot clinical data suggested that APT might provide useful visual information about the presence and grade of brain tumors (Jones et al., 2006; Zhou et al., 2008), based on increased cellular protein and peptide levels in gliomas (Hobbs et al., 2003; Howe et al., 2003). The APT sequence is similar to the routinely used magnetization transfer contrast (MTC) sequences in the clinic (Wolff and Balaban, 1989), and it can be performed on any standard MRI platforms, including 7 T (Mougin et al., 2010). The purpose of this study was to demonstrate that protein and peptide-based APT imaging could potentially enhance non-invasive identification of the heterogeneity of high-grade brain tumors, which is particularly important when gadolinium-enhanced T1-weighted MRI is not available.

Materials and methods

Study population

Twelve patients (nine male, three female; age range, 21–63 years; mean age, 42.9 years; see Table 1 for more information) with high-grade gliomas were included in this study. The studied neoplasms consisted of World Health Organization glioblastoma multiforme (grade IV astrocytoma) in four, grade III anaplastic astrocytoma in five, grade III anaplastic oligodendroglioma in one, the recurrence of grade III anaplastic astrocytoma in one, and the recurrence of grade III anaplastic oligodendroglioma in one. All diagnoses were confirmed by histopathology. The study was approved by the local ethics committee, and written, informed consent was obtained from each patient.

MR imaging

All patients were scanned on a Philips 3 T MRI scanner (Achieva 3.0 T; Philips Medical Systems, Best, The Netherlands) using a body coil for radiofrequency (RF) transmission and an eight-channel sensitivity-encoding coil for reception. The sequences performed for each patient included T1-weighted (repetition time = 2 s; echo time = 20 ms), T2-weighted (repetition time = 3 s; echo time = 80 ms), FLAIR (repetition time = 11 s; inversion time = 2.2 s; echo time = 125 ms), APT imaging, and gadolinium contrast-enhanced T1-weighted. For the routine MRI sequences, the field of view was 240×240 mm^2, the matrix was 512×512, and the slice thickness was 6 mm. After T1-weighted, T2-weighted, FLAIR, and APT scans were performed, 10 ml of gadopentetate dimeglumine (Magnevist; Bayer Schering, Guangzhou, China) was injected through the median cubital vein, and gadolinium-enhanced T1-weighted images were acquired.

It was shown previously (Zhou et al., 2008) that six-offset APT data acquisition (±3, ±3.5, ±4 ppm, 8 signal averages), together with a separately acquired *z*-spectrum (33 offsets from 8 to -8 ppm with intervals of 0.5 ppm, one average), could provide B0 inhomogeneity-corrected human brain APT images of sufficient signal-to-noise ratios within a clinically relevant time frame. In this study, a modified multi-offset, multi-acquisition APT imaging acquisition scheme (Table 2) was used, in which the APT image scan and *z*-spectrum scan were combined. To obtain the sufficient signal-to-noise ratios (~70; see the Discussion section) of the APT images, more acquisitions were placed at and around ±3.5 ppm. In addition, more offsets were used near 0 ppm for increasing the fitting accuracy of B0 maps; more offsets were used close to ±3.5 ppm for increasing the interpolation accuracy of APT data. Using the modified APT acquisition method, there was no need for the procedure to turn off the pre-scan between the two scans, which can affect the shim and frequency offset settings. The imaging parameters used were: RF saturation power = 3 μT; saturation time = 500 ms; repetition time = 3 s; echo time = 11 ms; sensitivity-encoding factor = 2; matrix = 128×64; field of view = 240×240 mm^2; and slice thickness = 6 mm. One unsaturated image (no saturation pulses added) was acquired for control. The scanning time for this APT scan was about 3 min.

Image analysis

All raw data were transferred to a Sun UltraSparc Station (Sun Microsystems, Mountain View, CA) for analysis, using programs written in interactive data language (IDL; Research Systems, Inc., Boulder, CO, USA). The definitions and nomenclature used in this study are equivalent to the previous papers (Jones et al., 2006; Zhou et al., 2008). Briefly, the magnetization transfer ratio (MTR) is defined as: $\mathrm{MTR}=1-S_{sat}/S_0$, in which S_{sat} and S_0 are the signal intensities with and without selective RF irradiation, respectively. The calculated MTR asymmetry (MTR_{asym}) map at the offset of 3.5 ppm is called the APT image: $\mathrm{MTR}_{asym}(3.5\ \mathrm{ppm})=\mathrm{MTR}(+3.5\ \mathrm{ppm})-\mathrm{MTR}(-3.5\ \mathrm{ppm})=S_{sat}(-3.5\ \mathrm{ppm})/S_0-S_{sat}(+3.5\ \mathrm{ppm})/S_0$. In the data processing (Fig. 1), the raw data were first organized into the *z*-spectrum. Then, the *z*-spectrum was fitted on a pixel-by-pixel basis according to the procedure previously reported (Zhou et al., 2008), and the B0 inhomogeneity map was created. After this, the original *z*-spectrum was corrected for the B0 inhomogeneity effect through the interpolation and centering of the *z*-spectrum. Finally, the APT image was calculated and displayed in color using a window of -5% to 5%.

The quantitative image analysis was performed by two radiologists (ZW and XW, who had ~20 and 10 years of experience in brain tumor imaging, respectively). The results were averaged for each tissue type for each subject. Five regions of interest were selected according to the signal abnormalities on the gadolinium-enhanced T1-weighted and other MR images, with the support of the histopathological findings. These regions of interest included the viable tumor core (with gadolinium enhancement or, if the gadolinium enhancement is not available, based on the FLAIR and T1-weighted MR images; see the Results section), necrosis (usually inside the lesion), cystic cavity (with the signal intensity similar to that of the cerebrospinal fluid on the T2-weighted images), immediate edema (adjacent to but distinct

Table 1
Patient characteristics and pathology.

No.	Age	Sex	Lesion location	Clinical presentation	Pathology
1	21	M	Right parietal	Headache	Astrocytoma, Grade III
2	45	M	Left parietal	Seizure	Recurrence of astrocytoma, Grade III
3	35	M	Left frontal	Seizure	Glioblastoma multiforme
4	46	F	Right frontal	Headache	Glioblastoma multiforme
5	61	M	Left frontal	Weakness of right limbs	Glioblastoma multiforme
6	63	M	Right temporal	Weakness of left limbs	Astrocytoma, Grade III
7	32	F	Left basal ganglia	Weakness of right limbs	Glioblastoma multiforme
8	34	M	Left temporal	Seizure	Recurrence of anaplastic oligodendroglioma, Grade III
9	47	F	Left occipital	Weakness of right limbs	Astrocytoma, Grade III
10	38	M	Left temporal	Weakness of right limbs	Astrocytoma, Grade III
11	43	M	Right parietal–occipital	Headache	Anaplastic oligodendroglioma, Grade III
12	50	M	Left parietal–occipital	Seizure and weakness of left limbs	Astrocytoma, Grade III

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