MRI assessment of acute cerebral ischaemia in rat using T1rho, diffusion, MT and amide proton transfer ratio (APTR)

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Introduction

Diffusion [1, 2] and $T_{1\rho}$ [3, 4] MRI reveal acute cerebral ischaemia within minutes after occlusion of feeding vessels. There is a growing body of evidence to show that initial diffusion failure due to ischaemia may transiently recover upon reperfusion regardless of long-term tissue outcome [5, 6]. In clinical settings, however, low cerebral diffusion coefficient is often associated with irreversible ischaemia [7]. It would be useful to have MRI contrasts available to identify acutely flow-compromised tissue, yet with a full potential of reversibility. $T_{1\rho}$ MRI has been shown to highlight ischaemic tissue almost immediately after cessation of flow [4] and importantly, during reperfusion $T_{1\rho}$ MRI changes correlate better with long-term tissue outcome than those provided by diffusion MRI. Recently, it was reported that a saturation transfer -based MR contrast, obtained by saturating amide region of the ^{1}H spectrum at 8.3 ppm (~3.5 ppm downfield the water peak), changes in the early moments of acute stroke [8]. Asymmetry in the Z spectrum, thought to reflect proton exchange between protein amide groups and water *in vivo*, has been exploited to quantify amide group concentration (an index of protein concentration and/or folding) [9] as well as the exchange rate [8]. In the present study interrelationship between diffusion, $T_{1\rho}$, MT and amide proton transfer ratio (APTR) in acute rat stroke induced by middle cerebral artery occlusion (MCAo) were investigated.

Methods

Male Wistar rats (250 to 310g, n=11) were anesthetized with 1% halothane in 70/30 N_2O/O_2 for MCAo [10] and MRI. Arterial blood gases and pH were analyzed during experiments and physiologic homeostasis was maintained as required. MRI experiments were performed in a horizontal 4.7T magnet interfaced to a Varian Inova console during MCAo (by 90 min) and reperfusion (by 120 and 150 min from the onset of MCAo). A quadrature half-volume coil was used as a transmitter and receiver. Diffusion, $T_{1\rho}$ and MT data were acquired in an interleaved manner using a linescan spin-echo sequence (TE 15 ms, line 3mm*3mm*35mm, 128 pixels along the line). The imaging line was positioned so that the centre of the coronal line was 4.1 mm from the surface of the brain and 3.8 mm caudally from the olfactory bulb covering the striatum and parietal cortex. D_{av} was quantified using a spin echo sequence incorporating four bipolar gradients along each axis [11] with four b-values from 0 to 1370 s/mm^2 (TR 2.5 s, TE 55 ms). The on-resonance $T_{1\rho}$ was quantified using five adiabatic spin-lock pulses ranging from 10 to 90 ms with a B_{1SL} = 0.6 G (TR 2.5 s, TE 15 ms). The Z spectra were acquired by saturating off-resonance frequencies with a train of 6.6 ms long 180^o Gauss pulses with interpulse delay of 3.4 ms for 4 s (offset frequencies of 0-2 kHz, TR = 7 s, TE = 15 ms) or with 5 s long CW pulse ($B_{1,CW}$ = 0.025 G, offset frequencies = ±6 kHz). MTR asymmetry (MTR_{asym}) was measured by subtracting S/S_0 from measurements with off-resonance saturation at 3.5 ppm and –3.5 ppm relative to the water peak. Change in proton transfer ratio (PTR) between ipsilateral and contralateral side (ΔPTR) was calculated and transformed to ΔpH_i using the calibration by Zhou et al. [8].

Results

Ischaemia caused a decrease in D_{av} by >20% in ipsilateral cortex and putamen and no recovery of D_{av} was detected upon reperfusion (Table I). $T_{1\rho}$ was prolonged by 90 min of MCAo, progressively increasing throughout the observation period, being elevated by ~20% by 150 min (Table I). Typical Z spectra from normal and ischaemic brain are shown (Fig. 1). Conventional MT measured with off-resonance frequencies at -6 kHz and 6 kHz showed slightly elevated values of S/S_0 in the ipsilateral side (Table I). Consistent with a previous report [8] MTR_{asym} ~3.5 ppm from the water peak significantly changed in the ischaemic brain (Fig. 2, Table I). ΔPTR between ipsilateral and contralateral side was different from zero at 90 min of MCAo, translating to a pH_i drop of 0.28 pH units (Table I), assuming that the pH change is the only factor contributing to the PTR. Interestingly, ΔPTR gradually normalized during reperfusion (Table I). A plot of $\Delta T_{1\rho}$ vs. ΔpH_i (from ΔPTR) at 90 min of MCAo showed no correlation between these two variables (Fig. 3).

Conclusions

These results show that acute stroke is associated with a decrease in ΔPTR. This effect is deduced to reflect decline in amide proton exchange rate due to acidosis. We estimate acidification of ~0.3 pH units from ΔPTR, which is much less (by ~ 50%) than that reported for normoglycaemic animals by ^{31}P NMR spectroscopy in acutely ischaemic brain [12]. It may well be that other factors, such as decline in temperature [6] and/or changes in relaxation times, may influence estimation of pH_i from ΔPTR. We observed no correlation between ΔPTR and $T_{1\rho}$ during MCAo suggesting that these MRI variables change independently in the ischaemic brain. Interestingly, ΔPTR shows normalization upon reperfusion in tissue displaying low D_{av} and $T_{1\rho}$ as signs of irreversible state. Thus, D_{av}, $T_{1\rho}$, MT and PTR provide a wealth of noninvasive information from acute stroke that may be potentially useful for the assessment of tissue viability in ischaemic diseases.

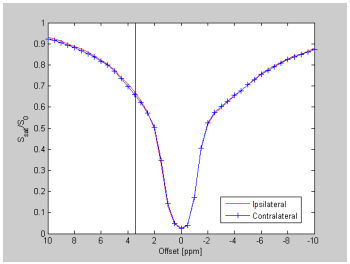

Fig.1: Typical Z-spectra (S_{sat}/S_0) from normal and ischaemic brain.

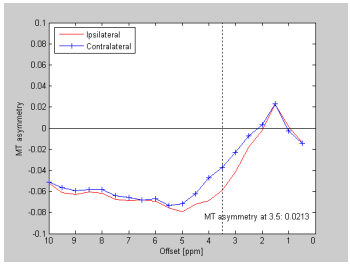

Fig.2: A representative case showing MTR asymmetry at ~3.5 ppm from water.

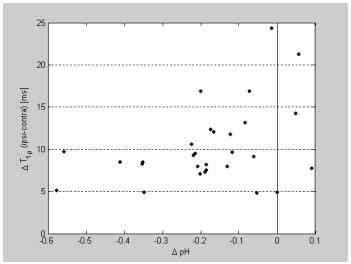

Fig.3: $\Delta T_{1\rho}$ plotted as a function of ΔpH_i.

Table I: Measured MR parameters from different time points (mean ± SEM, n = 11, with 6 controls). Significance between contralateral and ipsilateral values was tested by Student's t-test (*P<0.05, **P<0.01).

	D_{av} [*10^{-3} mm^2/s]		$T_{1\rho}$[ms]		ΔPTR	ΔpH	S/S_0 (-6kHz)		S/S_0 (6kHz)	
	Ipsi	Contra	Ipsi	Contra	(Ipsi-Contra)	(Ipsi-Contra)	Ipsi	Contra	Ipsi	Contra
Control	0.71±0.01	0.71±0.01	80.7±0.3	80.9±0.3	0.005±0.001	0.04±0.01	0.73±0.01	0.73±0.01	0.75±0.00	0.75±0.01
90min	0.51±0.01**	0.72±0.01	89.1±0.4**	81.1±0.5	-0.025±0.002**	-0.28±0.03**	0.73±0.01	0.72±0.01	0.75±0.01*	0.74±0.01
120min	0.53±0.02**	0.71±0.02	91.2±0.6**	81.2±0.6	-0.015±0.002**	-0.14±0.02**	0.73±0.01	0.72±0.01	0.76±0.01	0.74±0.01
150min	0.51±0.01**	0.72±0.01	94.4±1.0**	80.0±0.4	-0.008±0.002	-0.07±0.02	0.74±0.01	0.72±0.01	0.76±0.01*	0.74±0.01

References

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