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Does signal-attenuation on high-field T_2-weighted MRI of the brain reflect regional cerebral iron deposition? Observations on the relationship between regional cerebral water proton T_2 values and iron levels

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SUMMARY T_2-weighted MRI shows attenuated signals from the basal ganglia, such signal attenuation being more evident at high magnetic field strengths of 1·5 tesla (T). The basal ganglia contain high levels of iron, and it has been suggested that these iron deposits lead to shortening of bulk water T_2 protons via a mechanism involving diffusion of water through local magnetic field gradients generated by the iron. This mechanism generates a relaxation contribution that is proportional to the square of the applied static field B_o, and if it is significant the relaxation rate $1/T_2$ should be strongly dependent on B_o. T_2-weighted MRI would then provide a potential means of imaging regional cerebral iron levels at field strengths that are high enough for this mechanism to be important. The bulk water proton spin-spin relaxation times (T2) of samples from caudate nucleus, frontal cortex, and white matter, taken from fresh cerebral necropsy material of four subjects dying of non-neurological conditions, and one subject with Parkinson's disease have been measured. T_2 values were compared with regional cerebral iron content. At high field strengths (2·35 T and 8·5 T) no significant variation in regional cerebral water proton T_2 values was found; caudate, cortex and white matter had similar water proton spin-spin relaxation times in spite of the variation in their iron content. Increasing the field strength from 2·35 T to 8·5 T resulted in a generalised 50% decrease in mean regional cerebral T_2 values, as opposed to the 13-fold decrease expected if T_2 relaxation was dominated by a mechanism that is dependent on B_o^2. It was thus not possible to provide evidence that iron deposition per se is responsible for the attenuated signal obtained from the basal ganglia in T_2-weighted MRI.

Conventional magnetic resonance imaging (MRI) produces tomographic scans which can be weighted according to spin-lattice (T_1) or spin-spin (T_2) relaxation times of water protons. With T_2-weighted MRI in normal subjects, many of the central grey nuclei of the brain appear as regions of reduced signal.[1-3] This effect is more evident at higher static field strengths of 1·5 tesla (T) than lower field strengths such as 0·15 T.[3] The lowest levels of signal are obtained from globus pallidus and the zona reticulata of the substantia nigra. As these are the regions of the brain with the highest iron content this observation has led to the suggestion that high-field T_2-weighted MRI could be used as a means of assessing regional cerebral iron content.[1,2] While the intensities of the T_2-weighted MRI water proton signals are approximately inversely related to known regional cerebral levels of iron deposition, the correlation is imperfect; the putamen and caudate show little loss of signal despite high iron content, while internal capsule and corpus callosum show unexpectedly low signals.[4]

Using T_2-weighted MRI at higher field strengths, low signal from the putamen has been reported in patients with multi-system atrophy, progressive supra-

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nuclear palsy, Parkinson's disease, and multiple sclerosis.[2 3 5 6] This finding has been interpreted as reflecting increased iron deposition in the putamen in these four conditions.[2 5 6] Necropsy studies, however, have shown inconsistently raised iron deposition in the putamen in multiple system atrophy and in Parkinson's disease,[7-9] while involvement of the putamen in multiple sclerosis is rare.[10] Consequently an increase in putamen iron levels in multiple sclerosis would be surprising. It should be noted that decreased signal from the putamen in the T_2-weighted MRI brain scans of many elderly normal subjects has been reported, and so this finding is of questionable pathological significance.[3 4]

Assuming higher levels of iron content are responsible for the low signals obtained from some of the central grey nuclei in T_2-weighted MRI, a mechanism must be invoked by which the presence of iron leads to shortening of water proton T_2 values at higher field strengths while leaving their T_1 values relatively unaffected. Iron is stored in brain tissue as Fe^{III} bound to ferritin and metallothionenes.[15] The ferric ion is paramagnetic with five unpaired electrons. If water molecules are unable to bind close to ferric ions, but experience heterogeneous magnetic field gradients due to their presence, the water proton spin-spin relaxation rates ($1/T_2$), but not their spin-lattice rates ($1/T_1$), should increase in a manner proportional to the square of the static field strength (B^2) and to the concentration of paramagnetic ions present.[11-14]

The purpose of this study was to measure regional cerebral T_2 values of bulk water protons at different field strengths using fresh necropsy material. Caudate, frontal cortex, and central white matter regions were selected for study as uncontaminated specimens from these regions could be readily obtained. Such regions represent a spectrum of regional cerebral iron content. Water proton T_2 values were measured using nuclear magnetic resonance spectroscopy (NMR) at field strengths of 2·35 T and 8·5 T, field strengths far higher than those employed in clinical MRI. Using these high field strengths it was hoped to determine whether variations in regional cerebral iron content affect regional cerebral water proton T_2 values, and if so the nature of the field dependence of the iron effect.

Methods

(a) *Selection of necropsy material*

Brains were obtained from the Parkinson's Disease Society Brain Bank and Kings College Hospital, London. Four subjects who had died from non-neurological causes (liver failure, two with myocardial infarction, and pulmonary embolus) and one subject with long-standing Parkinson's disease (subsequently confirmed histologically) were examined. Material was preserved at 4°C and sampled within 48 hours of death. Specimens were taken from the head of caudate, the grey matter of the middle frontal gyrus, and the white matter of the centrum semiovale. Leptomeninges were stripped from cortical biopsy specimens, and all specimens were loaded into 5 mm outer diameter NNR tubes. Following NMR all samples were weighed and then dried to constant weight so that water content could be determined. Tissue samples adjacent to those areas selected for NMR were also taken and fixed in 10% formol-saline. These were then processed in paraffin wax for routine light microscopy. Sections were stained with haematoxylin and eosin, and with PERL's stain for iron.

Following NMR, dried specimens were sent for neutron activation analysis of iron, chromium, copper, cobalt, nickel and manganese levels. Analysis was performed by Dr G R Gilmore, University Research Reactor, Activation Analysis Service, Risley, Warrington, UK.

(b) *Nuclear magnetic resonance spectroscopy*

^1H NMR was performed at 100 MHz (2·35 T) and 360 MHz (8·5 T) using Bruker AM spectrometers. T2 was measured using a Hahn spin-echo sequence with TE values of 2, 4, 8, 12, 20, 40, 60, 80, 120, 160, 200 and 240 ms (at 8·5 T) and with additional TE values of 300, 360, 420 and 480 ms at 2·35 T.

EXORCYCLE phase cycling was used to suppress the effects of imperfections in the radiofrequency pulses. Caudate and frontal cortical biopsy material consistently yielded clearly defined T2 values for bulk water protons. Central white matter biopsy material occasionally yielded

Table 1 *Mean regional cerebral mineral content of biopsy material of the 5 subjects*

	(gx10⁶ per g dry tissue)		
	Caudate (mean, SD)	*Frontal Cortex (mean, SD)*	*Central White (mean, SD)*
Iron	578, 120 (520)	268, 36 (240)	151, 29 (154)
Copper	23, 6 (20)	20, 3 (18)	10, 1 (9)
Manganese	3·3, 1·0 (2·9)	1·5, 0·2 (1·5)	1·1, 0·3 (0·9)
Water content	85, 0·7	85, 1·0	70, 2·0

( ) levels in the Parkinsonian subject.

Table 2 *Regional cerebral bulk water T_2 spin-spin relaxation times as a function of field strength*

(a) 2·35 T (100 MHz)	T_2 (ms)		
Subject	*Caudate*	*Cortex*	*White*
1	84	79	63
2	75	88	76
3	56	91	80
4	58	97	76
PD	82	92	94
Mean	71, SD 13	89, SD 7	78, SD 11
(b) 8·5 T (360 MHz)	T_2 (ms)		
Subject	*Caudate*	*Cortex*	*White*
1	38	43	29
2	40	39	36
3	33	46	38
4	28	44	39
PD	36	40	40
Mean	35, SD 5	42, SD 3	36, SD 4

PD = Parkinson's Disease

two T2 values suggesting bulk water compartmentation. When this occurred the shorter T2 value, which was the major component, was used for comparison.

Results

Table 1 shows the mean regional cerebral iron, copper and manganese levels for the biopsy material from the four non-neurological subjects and the Parkinsonian patient. The individual regional cerebral mineral levels of the Parkinsonian patient did not differ significantly from the values of the other subjects. Cobalt, nickel and chromium were present in insignificant quantities.

It can be seen that the ratios of iron content per dry weight of brain tissue were approximately 4:2:1 for caudate:cortex:white matter. Copper and manganese levels were also highest in the caudate nucleus. PERL staining showed a similar regional cerebral distribution of iron in all five subjects, at low magnification the iron appearing evenly distributed throughout each cerebral structure. There was no difference in the iron distribution in the regions studied between the patient with Parkinson's disease and the other subjects. Higher magnification showed deposits of iron in and around vessels, and in the perikarya of oligodendrocytes.

Table 2 shows individual and mean regional cerebral water proton T_2 values for the five subjects at field strengths of 2·35 T and 8·5 T. Increasing the static field strength from 2·35 T to 8·5 T, that is, by a factor of 3·6, led to a generalised 50% reduction in mean regional cerebral water proton T_2 values. At individual field strengths of 2·35 T and 8·5 T no significant difference was found between mean water proton T_2 values of caudate, cortex and white matter, in spite of the variation in their iron content.

Discussion

It has been proposed that the attenuated signals obtained from the basal ganglia in high-field T_2-weighted MRI of the brain arise from shortening of bulk water proton T_2 values due to local magnetic field inhomogeneities.[1 2 5] These field inhomogeneities are said to result from the increased levels of iron present in the basal ganglia, this iron leading to variations in tissue magnetic susceptibility. If the iron generates relaxation via a mechanism involving diffusion of water molecules through local field gradients, then the regional cerebral water proton relaxation rates $1/T_2$ should increase according to B_o^2 and to the regional cerebral iron concentration.[11-14] Our findings show that at field strengths of both 2·35 T and 8·5 T there was no significant regional variation in mean cerebral water proton T_2 values, caudate, cortex, and white matter yielding similar results (see table 2) in spite of the variation in their iron content. Increasing the field strength from 2·35 T to 8·5 T resulted in a generalised 50% reduction in mean regional cerebral water proton T_2 values, whereas a 13-fold, that is, $(8{\cdot}5/2{\cdot}35)^2$-fold, reduction would have been expected if diffusion through field gradients generated the dominant relaxation mechanism. Our findings therefore argue against this mechanism being responsible for the low signals obtained from the basal ganglia in T_2-weighted MRI.

In general, relaxation of water protons will contain contributions from both diamagnetic and paramagnetic mechanisms. The presence of paramagnetic species can affect water proton NMR signal intensities by several different mechanisms.[1] Although our results argue against diffusion through field gradients as being the dominant mechanism leading to reduction of water proton T_2 values in certain diencephalic nuclei, they do not exclude the possible contribution of other mechanisms that have a small dependence of T_2 on field strength such as those operating via the direct binding of water to ferric ions. In addition, our findings do not exclude local variations in magnetic susceptibility being the cause of the signal attenuation seen in T_2-weighted MRI scans of cerebral haematomas, though the field dependence of this signal attenuation appears to depend on the precise pulse sequence that is employed.[16 17]

In conclusion, while there is no doubt that certain central grey nuclei show attenuated signal on T_2-weighted MRI, it remains to be proven that this attenuation is a direct consequence of the presence of iron deposits.

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