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FULL PAPER

T1ρ relaxation time in brain regions increases with ageing: an experimental MRI observation in rats

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Objective: T1ρ variation is associated with neurodegenerative diseases. This study aims to observe T1ρ relaxation time changes in rat brains associated with normal ageing in Sprague-Dawley (SD) rats, Wistar Kyoto (WKY) rats and spontaneously hypertension rats (SHRs).

Methods: 18 male SD rats, 11 male WKY rats and 11 male SHRs were used. T1ρ measurement was performed at 3-T MR with a spin-lock frequency of 500 Hz. SD rats were scanned at the ages of 5, 8, 10 and 15 months. SHRs and WKY rats were scanned at the ages of 6, 9 and 12 months.

Results: For SD rats, T1ρ at the thalamus, hippocampus and frontal cortices increased significantly from 5 to 15 months ($p < 0.05$). For the WKY rats and SHRs, the

T1ρ values in the thalamus, hippocampus and frontal cortices also increased significantly from 6 to 12 months ($p < 0.05$). Furthermore, T1ρ in the thalamus, hippocampus and frontal cortices of SHRs were consistently higher than those of WKY rats at the ages of 6, 9 and 12 months ($p < 0.05$). The percentage regional T1ρ differences between WKY rats and SHRs did not change during ageing.

Conclusion: An increase in T1ρ was associated with age-related changes of the rat brain.

Advances in knowledge: An age-related and hypertension-related T1ρ increase in rat brain regions was observed in the thalamus, hippocampus and frontal cortical regions of the rat brain.

INTRODUCTION

T1ρ experiments have the potential to provide information about the low frequency motions (100 Hz to a few kilohertz) in biological systems.¹ T1ρ relaxation not only depends on T_1 and T_2 but also has contributions from several MR interactions such as chemical exchange, dipolar interaction and J-coupling. Depending upon the tissue type, more than one mechanism may be operative simultaneously but with different relative contributions. During recent years, the potential applications of T1ρ MRI have been studied, covering various organs and a wide range of disease processes.^{2–13} T1ρ variation has been also reported to be associated with a number of neurodegenerative diseases and has potential to be an early biomarker for cerebral ischaemia. Borthakur et al¹⁴ measured the T1ρ of plaque burden in a mouse model of Alzheimer's disease (AD). In one clinical study, T1ρ was measured on patients with AD, mild-cognitive impairment and in age-matched cognitively normal control subjects.¹⁵ A statistically significant increase

in both the grey matter and white matter in the medial temporal lobe was seen in patients with AD over age-matched controls. In some following studies, increased T1ρ was similarly found in AD and mild-cognitive impairment cohorts compared with normal control subjects.^{16–18} Nestrasil et al¹⁹ reported that compared with controls, the substantia nigra of subjects with Parkinson's disease (PD) had also increased T1ρ. Haris et al¹⁸ measured T1ρ in the hippocampus in the brain of control patients and those with AD, PD, and PD and dementia. They found that the serial measurement of T1ρ in both AD and PD provides information on disease progression and contributes to early diagnosis. T1ρ has also been investigated as a MRI indicator of cerebral ischaemia.^{20–24}

Ageing and hypertension are two common risk factors for neurodegenerative diseases. Decrease of cerebral blood flow,²⁵ brain atrophy^{26,27} and loss of nerve cells²⁸ are commonly seen in the brains of aged rats. Spontaneously

Figure 1. T1 ρ MR scan schedule for animals. SD, Sprague-Dawley; SHR, spontaneously hypertension rat; WKY, Wistar Kyoto.

hypertension rats (SHRs) are normotensive at birth and gradually develop severe hypertension in the first 2–4 months of life. At 6 months, they develop a sustained hypertension compared with their normotensive control strain, the Wistar Kyoto (WKY) rats.^{27–31} The hypertensive rats exhibit brain changes similar to ageing rats^{27–30} but can be more advanced than the age-matched normative rats. In this study, we aimed to investigate the changes of T1 ρ values in rat brains associated with normal ageing process in Sprague-Dawley (SD) rats, WKY rats and SHRs.

METHODS AND MATERIALS

Animals

The protocols and procedures were approved by the local animal experimentation ethics committee. Rats were provided by the Laboratory Animal Services Centre of The Chinese University of Hong Kong. 18 male SD rats, 11 male Wistar Kyoto WKY rats and 11 male SHRs were used in the study. Two to three animals were housed per stainless steel cage on a 12-h-light/12-h-dark cycle in an air-conditioned room at 22°C, and checked daily by the animal care staff. A standard commercial rat chow (Prolab RMH 2500; PMI Nutrition International LLC, Brentwood, CA) and water were available *ad libitum*. The SD rats were MR scanned longitudinally at the age of 5, 8, 10 and 15 months (Figure 1). The SHRs and age-matched WKY rats were MR scanned longitudinally at the age of 6, 9 and 12 months (Figure 1). For MRI examinations, the rats were anaesthetized using a combination of xylazine (10 mg kg⁻¹) and ketamine (90 mg kg⁻¹).

MRI protocol

MRI was performed using a 3-T clinical MR system (Achieva®; Philips Healthcare, Best, Netherlands). After anaesthesia, animals were positioned prone and a custom-made quadrature volume radiofrequency coil with 7-cm internal diameter was used as both signal transmitter and receiver.

For T1 ρ measurement, a rotary echo spin-lock pulse³² was implemented in a three-dimensional balanced fast field echo (bFFE, also known as balanced steady-state free precession) sequence.³³ The pulse sequence started with a fat-suppression module using a spectrally selective radiofrequency pulse and the associated gradient spoilers and was then followed with a rotary echo spin-lock pulse for T1 ρ preparation. In the bFFE preparation module, a half-alpha pulse and four start-up pulses with dummy data acquisitions were used to approach the steady-state but with T1 ρ -weighted magnetization maintained. The subsequent segmented normal phase alternating bFFE readout with centric phase-encoding order was used for acquisition. The shot length was 40 ms, and a TI (inversion time) after each shot acquisition was set to 5500 ms to restore equilibrium magnetization before the next T1 ρ preparation. Spin-lock frequency was set to 500 Hz. Echo time and repetition time were 3.6 and 7.4 ms, respectively. The voxel size was 0.3 × 0.35 × 1.50 mm³. The flip angle was 40°.

The images of SD rats were acquired with three spin-lock times (TSLs) of 1, 20 and 50 ms.^{34–36} The MR images of SHRs and WKY rats were acquired at four TSLs of 1, 20, 50 and 80 ms. The number of signal average was three for SD rats and four for SHRs and WKY rats. For the SD rats, an inversion turbo field echo (TFE) prepulse (inversion time, 1700 ms) was used to remove the contribution from the cerebrospinal fluid to the T1 ρ maps, but this was not used in SHRs and WKY rats. 14–16 axial slices were scanned to cover the whole rat brain.

Data processing

T1 ρ maps were computed on a pixel-by-pixel basis using a monoexponential decay model of $M(TSL) = M_0 \times \exp(-TSL/T1\rho)$ with a home-made MATLAB® program (MathWorks®, Natick, MA), where M_0 and $M(TSL)$ denote the equilibrium magnetization and the T1 ρ -prepared magnetization with the spin-lock

Figure 2. T1 ρ weighted images of a Sprague-Dawley rat with spin-lock time (TSL) of 1, 20 and 50 ms. Fluid attenuation technique was applied. The bilateral thalamus (T), hippocampus (H) and cortices (C) were manually defined on the T1 ρ map.

Figure 3. T1ρ weighted images of a spontaneously hypertension rat with spin-lock time (TSL) of 1, 20, 50 and 80 ms. Fluid attenuation technique was not applied. The bilateral thalamus (T), hippocampus (H) and cortices (C) were manually defined on the T1ρ map.

time of TSL, respectively. This monoexponential equation was linearized by taking the natural logarithm, and then T1ρ maps were generated produced by fitting all pixel intensity data as a function of TSL time using least-square linear fitting. A typical T1ρ map of a SD rat generated by the T1ρ-weighted images acquired with the TSLs of 1, 20 and 50 ms is shown in Figure 2. A typical T1ρ map of a SHR rat generated by the T1ρ-weighted images acquired with the TSLs of 1, 20, 50 and 80 ms is shown in Figure 3.

Measurement and statistical analyses

These measurements were performed in the thalamus, hippocampus and cortical regions of the brain that are primarily associated with neurodegenerative disease.^{37,38} T1ρ values were measured in the user-defined regions of interest in the bilateral thalamus (T), hippocampus (H) and frontal cortices (C) from the T1ρ map of rat brains (Figures 2 and 3). The machine-related scan-rescan T1ρ measurement stability for small animals has been established previously.⁴ To assess interreader measurement reproducibility, 16 SD rats at 8 months were randomly selected, and the same data sets of the thalamus, hippocampus and frontal cortices were measured by two readers independently and intraclass correlation coefficient computed. Our statistical test showed that there was no significant difference in T1ρ values when comparing the two hemispheres. Therefore, we pooled the data of the corresponding regions of both hemispheres, *i.e.* the measurement from the left and right hemispheres were averaged, and one region from one animal would have one value for statistical analysis. Data are presented as mean ± standard deviation. All statistical analyses were performed using SPSS® 14.0 (IBM Corporation, Armonk, NY; formerly SPSS Inc., Chicago, IL). The Mann-Whitney *U* test was

used for non-paired comparison. The one-way analysis of variance test and Bonferroni adjustment for multiple comparisons were used in comparing T1ρ values with ageing process. A *p*-value <0.05 was considered statistically significant.

RESULTS

Two SD rats died at the age of 14 months because of ageing. The imaging data of one WKY rat at the age of 6 months, two WKY rats and one SHR at the age of 9 months, and two SHRs at the age of 12 months were not included in the analysis because of imaging failure, *i.e.* animals moved during the scanning (Figure 1). With the T1ρ results of the 16 SD rats measured by the two readers, the interreader intraclass correlation coefficient for the thalamus, hippocampus and cortices was 0.751, 0.794 and 0.735, respectively, indicating satisfactory interreader reproducibility.

The longitudinal T1ρ relaxation time data for SD rats are presented in Figures 4–6. At the age of 5 months, T1ρ of the thalamus, hippocampus and cortices was 67.2 ± 2.4 , 73.2 ± 2.3 and 71.6 ± 1.9 ms, respectively. By the age of 8 months, T1ρ in the thalamus, hippocampus and cortices increased by 5.1% ($p < 0.05$), 9.7% ($p < 0.05$) and 5.2% ($p < 0.05$), respectively, compared with the values at 5 months. At 10 months, T1ρ values in the thalamus, hippocampus and cortices increased by 5.8% ($p < 0.05$), 5.7% ($p < 0.05$) and 6.4% ($p < 0.05$), respectively, compared with the values at 8 months. At 15 months, T1ρ values in the thalamus, hippocampus and cortices further increased by 7.5% ($p < 0.05$), 5.7% ($p < 0.05$) and 6.6% ($p < 0.05$), respectively, compared with the value at 10 months, as well as increased by 19.5%, 22.4% and 19.4%, respectively, compared with the values at 5 months. One-way analysis of

Figure 4. T1ρ values in the thalamus (left), hippocampus (middle) and cortices (right) of Sprague-Dawley rats at the age of 5, 8, 10 and 15 months *** $p < 0.001$, ** $p < 0.01$. $p < 0.05$ for linear trend effect during the ageing process from 5 to 15 months.

Figure 5. One presentation of brain T1 ρ map of one Sprague-Dawley (SD) rat at 5, 8, 10 and 15 months (M). Note the cerebral ventricle size is small in SD rat.

variance test for linear trend showed that T1 ρ in the thalamus, hippocampus and cortices had a significant increasing trend during the ageing process from 5 to 15 months ($p < 0.05$).

The longitudinal T1 ρ relaxation time data for WKY rats and SHRs are presented in Figures 6–8. For the WKY rats and SHRs, the T1 ρ values in the thalamus, hippocampus and cortices had a significant linear increasing trend during the ageing process from 6 to 12 months ($p < 0.05$). At the age of 12 months, T1 ρ values in the thalamus, hippocampus and cortices of WKY rats increased by 20.0% ($p < 0.05$), 9.5% ($p < 0.05$) and 8.5% ($p < 0.05$), respectively, compared with the values at 6 months. Similarly, at the age of 12 months, T1 ρ values in the thalamus, hippocampus and cortices of SHRs increased by 14.7% ($p < 0.05$), 8.7% ($p < 0.05$) and 7.5% ($p < 0.05$), respectively, compared with the values at 6 months. Furthermore, T1 ρ values

in the thalamus, hippocampus and cortices of SHRs were consistently higher than those of WKY control rats at the ages of 6, 9 and 12 months. At the age of 6 months, T1 ρ values in the thalamus, hippocampus and cortices of SHRs were 12.6% ($p < 0.05$), 7.7% ($p < 0.05$) and 8.9% ($p < 0.05$) higher than those of WKY rats. At the age of 9 months, T1 ρ values in the thalamus, hippocampus and cortices of SHRs were 4.7% ($p < 0.05$), 4.7% ($p < 0.05$) and 5.2% ($p < 0.05$) higher than those of WKY rats. At the age of 12 months, T1 ρ values in the thalamus, hippocampus and cortices of SHRs were 7.0% ($p < 0.05$), 7.0% ($p < 0.05$) and 7.9% ($p < 0.05$) higher than those of WKY rats. The percentage regional T1 ρ values difference between WKY rats and SHRs did not change with the ageing process. It was noted that the cerebral ventricle size was larger in SHRs than in WKY rats, and the ventricle size became larger as the rats aged (Figure 8).

Figure 6. The mean plot of T1 ρ values for Sprague-Dawley (SD) rats (left), Wistar Kyoto (WKY) rats (middle) and spontaneously hypertension rats (SHRs) (right) at the different ages. For SD rats, $\Delta\%$ = (mean measured value at 15 months – mean measured value at 5 months)/mean measured value at 5 months. For WKY rats and SHRs, $\Delta\%$ = (mean measured value at 12 month – mean measured value at 6 months)/mean measured value at 6 months.

Figure 7. T1ρ values in the thalamus, hippocampus and cortices of Wistar Kyoto (WKY) rats and spontaneously hypertension rats (SHRs) at the age of 6 (left), 9 (middle) and 12 months (right). *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. $p < 0.05$ for linear trend effect during the ageing process from 6 to 12 months.

DISCUSSION

The diagnosis and therapy of age-related chronic diseases will become more and more challenging in the course of the next few decades because the percentage of elderly people is increasing. Classic symptoms of the neurodegenerative diseases include memory loss, confusion and biological features such as the formation of neurofibrillary tangles, senile plaques of amyloid- β protein and grey matter atrophy. Both normal ageing processes and neurodegenerative disorders are accompanied by a critical reduction in the regional cerebral blood flow in brain regions, accompanied by grey matter and white matter hypodensity, and cerebral atrophy that may correlate with cognitive decline.^{39–41} Previous studies suggested that

neurodegeneration may contribute to the increased T1ρ relaxation in brain regions.^{16–19} For example, cerebral atrophy, which reflects underlying neuronal loss, has been reported to be associated with the increased T1ρ values in the hippocampus and medial temporal lobe of AD.¹⁶ It is also possible that normal ageing process may alter relative volume fractions of water and protein in brain tissue, and this will be reflected by the changes of T1ρ relaxation time. It is important to gain more information about age-related changes in T1ρ relaxation, because such data are not only needed to gain a deeper understanding of brain ageing but also to use as a normative data set for examinations performed with T1ρ MRI in patients and animals of different ages.⁴²

Figure 8. One presentation of brain T1ρ map of one Wistar Kyoto (WKY) rat and one spontaneously hypertension rat (SHR) at 6, 9 and 12 months (M), respectively. Note the cerebral ventricle size is larger in SHR than in WKY rat, and the cerebral ventricle size became larger as the rats aged.

Our results suggest that a T1 ρ increase was associated with ageing in brain regions of all SD rats, WKY rats and SHR. Brain regions of SHRs showed higher T1 ρ value than those of the control WKY rats. This is likely to be due to the hypertension-related changes of the rat brain. Hypertension is a prevalent comorbid medical condition of ageing and may also predispose to neurodegenerative disorders.⁴⁰ SHRs, which are normotensive at birth and develop sustained hypertension between 3 and 6 months of age, represent a model for hypertensive-related brain damage.²⁷ In 6- to 7-month-old SHRs, the ventricular volume can be two-fold greater than in WKY control rats.⁴³ Larger ventricular size was noted in SHRs than in WKY rats. Age-related ventricular enlargement was seen in both WKY rats and SHRs, although precise quantification was not carried out, as this was not the aim of this study. It has been shown that hypertensive rats exhibit similar brain changes as ageing rats, including the cerebral atrophy and loss of nerve cells,^{27–29,44} but these changes are more advanced than in normative rats. The higher degree of cerebral atrophy and loss of nerve cells might contribute to the higher T1 ρ values in SHRs than those of WKY rats.

There are a few limitations in this study. T1 ρ data acquisition techniques were different between those for SD rats and those for WKY and SHRs. SD rats underwent T1 ρ MRI with an inversion TFE prepulse inserted before T1 ρ pulse in order to remove the contribution from CSF to the T1 ρ maps. For SHR and WKY rats, no such inversion TFE prepulse was inserted before the T1 ρ pulse used, as it was found that this inversion pulse was not allowed at the TSL of 80 ms, probably due to the hardware restriction on our MRI scanner. In addition, three spin-lock times (TSL = 01, 20, 50 ms) and number of signal averaging (NSA) = 3 were used for SD rats; four spin-lock times (TSL = 01, 20, 50, 80 ms) and NSA = 4 were used for SHRs and WKY rats. The additional NSA was applied to compensate for the reduced image signal-to-noise ratio associated with the longer TSL of 80 ms. However, since the same protocol was used

longitudinally for all SD rats, as well as for all WKY rats and SHRs, this would not have affected the trend of changes, *i.e.* the increase of T1 ρ during ageing, and would not have affected the comparison between WKY and SHRs. On the other hand, our data indeed suggested different data acquisition techniques revealed similar trend of T1 ρ increase associated with the ageing process. Another limitation is that we did not scan the SHRs before the development of hypertension, therefore the relationship between T1 ρ increase and hypertension remains speculative. Further studies are warranted to clarify this point. It is expected that with the development of faster and more robust T1 ρ techniques, T1 ρ MR can be more widely applied in neuroimaging.^{37,38,45–48}

In conclusion, an increase in T1 ρ relaxation time was associated with age-related changes of the thalamus, hippocampus and frontal cortical regions of rat brain. A possible hypertension-related T1 ρ increase in rat brain regions was also noted. Although the biophysical/biochemical mechanism of ageing-associated T1 ρ increase remains to be further investigated, together with other novel MRI techniques, such as chemical exchange saturation transfer and its variant chemical exchange imaging with spin-lock technique, these techniques might provide an early imaging biomarker for neurodegeneration diseases including AD, PD and dementia.^{47,48} The age-related changes in T1 ρ relaxation should also be taken into account in longitudinal studies in rodents. Further validation of ageing-associated T1 ρ increase *in vivo* in the human brain is highly desired.

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