

Longitudinal Assessment of Brain Damage in Hypertension Rats Using Diffusion Tensor Imaging

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Synopsis

The elevated blood pressure is considered to be the main risk factor of stroke and is highly associated with white matter lesions. This study aimed to investigate the change of white matter microstructure under various levels of blood pressures.

Introduction

Hypertension is the leading risk factor of stroke (1). The spontaneous hypertensive stroke-prone rat (SHRSP) is generally considered a good experimental model for studying the hypertensive damage leading to stroke because its pattern of brain injury is similar to that in human stroke (2). SHRSP originated from selective inbreeding of spontaneously hypertensive rats (SHR), which has moderate blood pressure compared to SHRSP, while SHR were developed to be hypertensive by selective inbreeding of normotensive Wistar Kyoto rats (WKY). The model has been extensively used to study vascular alteration both structurally and functionally (3). However, a few studies have investigated the white matter (WM) damage in hypertensive rats. It has been suggested that the presence of cerebral white matter lesions (WMLs) in hypertension patients is important for the development of stroke. Moreover, the presence of WMLs is also an important prognostic factor for the development of stroke (4). Diffusion tensor magnetic resonance imaging (DTI) has been proved to be a promising method for characterizing microstructural changes in WM and has been widely used in many diseases investigating WM impairment such as stroke, brain trauma, and multiple sclerosis. The aim of this study is thus to explore the development of white matter damage using DTI in hypertensive rats, SHRSP and SHR, and their normotensive reference strain WKY rats.

Material and Methods

Three groups of male rats were studied including normotensive WKY and hypertensive SHR and SHRSP. SHRSP rats (4 weeks of age; n=4) were purchased from Charles River Laboratory (USA), while SHR rats (n=5) and WKY (n=5) at the age of 4 weeks were obtained from National animal center (Taipei, Taiwan). Mean systolic blood pressure was measured by tail-cuff method (MK-2000ST; Muromachi Kikai Co. Ltd., Tokyo, Japan). All images were performed on a 4.7-T Biospec 47/40 MR scanner and were measured at the rat age of 4, 12, 24, and 36 weeks. The rat was initially anesthetized with 5% isoflurane at 1L/min air flow. When fully anesthetized, the animal was placed in a prone position and fitted with a custom-designed head holder inside the magnet. Isoflurane was then maintained with 1~1.2% at 1L/min air flow throughout the experiments. Images were acquired using a 72-mm birdcage transmitter coil and a separate quadrature surface coil for signal detection. T2WI was acquired using a FSE sequence with a TR of 4500 ms, a TE_{eff} of 82 ms, an ETL of 8, a slice thickness of 1 mm, a FOV of 3 cm, data matrix size 256×128 (zero-filled to 256×256), and 8 averages. A spin echo, diffusion-weighted sequence was employed to perform DTI. The acquisition parameters were TR = 1.5 sec, TE = 31 msec, Δ = 15 msec, δ = 6 msec, slice thickness = 1 mm, FOV = 3 cm, data matrix size 128×128 (zero-filled to 256×256), and 4 averages. The six diffusion sensitizing gradient orientations along [G_x, G_y, G_z] were [1,1,0], [1,0,1], [0,1,1], [-1,1,0], [0, -1,1], and [1,0, -1]. The b-values used were 0 and 1100 sec/mm². Quantitative DT indices including relative anisotropy (RA), mean diffusivity (Tr), axial diffusivity (λ_{||}), and radial diffusivity (λ_⊥) were calculated pixel-by-pixel using an in-house software written by Matlab.

Results and Discussion

The mean systolic blood pressure in hypertensive SHR and SHRSP rats was at 140 and 220 mmHg, respectively, and in normotensive WKY rat was at 110 mmHg (Fig. 1). Figure 2 shows the T2WI of the representative rats of WKY, SHR, and SHRSP at the age of 4, 12, 24, and 36 weeks. No brain lesion can be found in WKY and moderate blood pressure of SHR until to the age of 36 weeks. Abnormal hyperintensity of T2WI showing brain damage was first observed at 24 weeks in SHRSP. In 36 weeks, whole SHRSP brain filled with the hyperintense regions and started to distort, suggesting more severe brain injury. DTI parameters further demonstrate the white matter deformation and loss of SHRSP brain at 36 weeks (Fig. 3). Quantitative analysis of DTI parameters in corpus callosum-external capsule shows the evident increase of diffusion anisotropy in all three animal strains at the age of 12 weeks compared to 4 weeks and it reaches a plateau after 12 weeks in both WKY and SHR rats (Fig. 4), while the significant anisotropy loss was found after 24 weeks in SHRSP rats. We further examine the other DTI parameters, the increase of RA with the decrease of λ_⊥ in all animal strains at 12 weeks is probably due to the WM development with the new formation of myelination. The decline of diffusion anisotropy with the rise of λ_⊥ in SHRSP brain after 24 weeks may attribute to the WM demyelination.

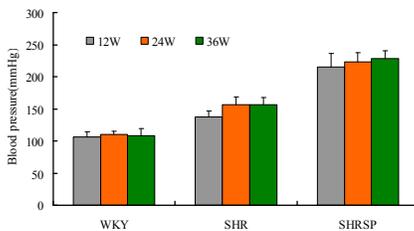


Fig. 1 The development course of systolic blood pressure in WKY, SHR, and SHRSP rats

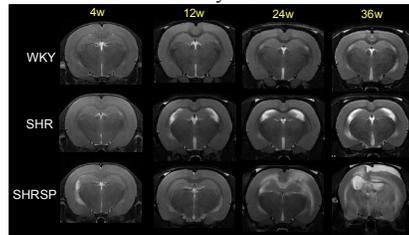


Fig. 2. Representative T2WI of WKY, SHR, and SHRSP in the age of 4, 12, 24, 36 weeks.

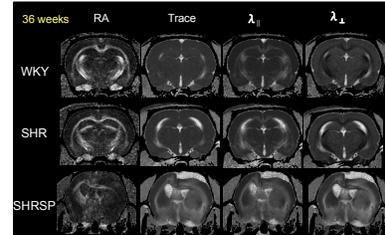


Fig. 3 Representative DTI maps (RA, Trace, λ_{||}, λ_⊥) in SHRSP rat at 36 weeks.

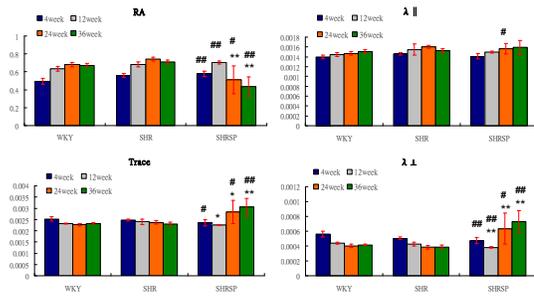


Fig. 4 Quantitative analysis of DTI parameters over time in corpus callosum-external capsule region

Conclusion

The current study demonstrates that the temporal variations of T2WI and DTI parameters in WKY, SHR, and SHRSP should greatly improve our understanding of blood pressure-related change in microstructural architecture of brain tissue.

Reference

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