MRI of the Neurological Effects in a Rat Model of Hypertension

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Introduction

It is well established that hypertension (HTN) in humans can lead to regional brain atrophy and cognitive decline. With a high prevalence in the community-dwelling elderly population, HTN may be an important factor influencing the development and progression of cognitive aging. We sought to investigate the effects of HTN on cognitive performance in a rat model and correlate them to findings from susceptibility weighted imaging (SWI), diffusion tensor imaging (DTI) and T2-weighted high-resolution anatomical MRI. Since the onset and progression of HTN in humans often occurs gradually after middle-age, we used transgenic rats that allow for the gradual induction of HTN in middle-aged animals [1].

Methods

The Cyp1a1 rats have the cytochrome P450 promoter inserted to up-regulate the expression of the mouse renin (Ren-2) gene. Administration of 0.15% indole-3-carbinol (I3C) to their chow activates the promoter to induce a gradual onset of HTN. I3C augmented diet was initiated at 16 months of age over a 6-week interval to produce a HTN group of Cyp1a1-Ren-2 rats (N = 9), whereas a control group of transgenic rats (NTN, N = 8) received normal chow. Learning and memory of rats were tested on the spatial and visually cued versions of the Morris swim task where a corrected integrated path length (CIPL) is inversely related to performance. MR Imaging was carried out following the 6 week period on a Bruker 7T BioSpec employing a 72 mm birdcage coil for excitation and a 4-channel phased array surface coil for reception. Whole brain SPGR and T2-weighted 3D-FSE images were acquired with 150 μm isotropic voxel resolution. DTI was carried out in 1 mm coronal sections (0.3 mm in plane) using a single-shot EPI with diffusion weighting (b = 1000 s/mm²) in 25 non-collinear directions. SWI images were produced by multiplying the magnitude SPGR images by a phasemask between 1 and 8 times [2]. ADC and FA maps were generated using standard algorithms in FSL. Multivariate network analysis with voxel-based morphometry (VBM) and the Scaled Subprofile Model (SSM; [2]) was used to identify a regional network pattern of MRI gray matter that differed between the groups.

Results and Discussion

During the 6-week treatment interval, the HTN group had higher mean systolic (187±13 mmHg; p < 5.76e-4) and diastolic (133±11 mmHg; p < 0.0079) blood pressure compared to the control group (156±13 mmHg and 111±13 mmHg, respectively). On the Morris Swim task, a significant main effect was observed for group (p < 0.01), with the hypertensive rats showing poorer performance than the control rats (Fig 1). ROI analysis of the SWI data showed differences in the groups within certain brain regions that approached significance with increasing susceptibility weighting (i.e. increasing number of phasemask multiplication). ROI analysis of the DTI data showed significant FA reductions in the corpus callosum of the HTN rats. The SSM analysis of gray matter maps generated from T2-weighted MRI identified a network pattern which distinguished the HTN rats from controls (p < 5.7e-4; Panel D). This pattern was characterized by reductions in regions of the temporal cortex, basal ganglia, cerebellum, and hippocampus, with areas of relative increases reflecting preservations in the frontal, somatosensory, and motor areas.

Conclusion

These findings provide support for the use of the Cyp1a1-Ren-2 rat and neurological MRI to advance translational research on the cerebrovascular effects of HTN during aging and may aid efforts in the evaluation of new treatments and prevention therapies for the brain changes associated with healthy and pathological aging.

References