Changes in White-matter Integrity and Evoked fMRI Responses in Chronic Hypertension

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Target Audience: neuroscientists and hypertension researchers

PURPOSE: Chronic hypertension has negative consequences on white matter and its development. The goal of this study was to evaluate white-matter changes in an established rat model of hypertension (SHR) at different stages of the disease progression. Comparisons were made with age-matched normotensive Wistar Kyoto (WKY) rats.

METHODS: Four groups of rats were studied: 10-week (N=6, 8~10 weeks) and 40-week (N=8, 38~40 weeks) old SHR rats, and the corresponding two age-matched WKY control groups with N=6 each. Body weight, heart rate and tail mean-arterial-blood pressure (MABP) in awake conditions were measured before each MRI section. Hypercapnic challenge for CR study used 5% CO2.

MRI was performed on an 11.7-Tesla Bruker Biospec scanner with a surface coil for brain imaging and a neck coil for arterial-spin labeling. DTI employed a spin-echo EPI with 3s TR, 29ms TE, 5.6x25.6mm^2 FOV, 96x96 matrix, 8 1.5-mm slices, and 8 averages. CBF employed continuous ASL with four-shot, gradient-echo planar imaging with 25.6x25.6cm^2 FOV, 96x96 matrix, 8 1.5-mm slices, TE=12ms, TR=3s per shot, and 60 repetitions. Fractional anisotropy was computed.

Coronal sections (60 μm) underwent Black-Gold staining for white matter. Immunohistochemistry Analysis with Image-Pro Premier SoftwareVersion 6.0. Behavioral (open field) tests were measured as an index of hyperactivity and water maze used for estimating the memory. T-test was used for comparison between different groups. A p value of 0.05 was taken to be statistically significant. Data showed in figures and texts are mean ± SEM.

RESULTS: WKY body weight and MABP increased significantly from 10 to 40 weeks of age, but heart rate did not change with age. Body weight was not statistically different between SHR and WKY at all stages. Differences in heart rate and MABP between SHR and age-matched WKY were present at 10 weeks, and grew progressively larger with age.

Figure 1 shows an FA map and the typical ROI used in quantitative analysis: corpus callosum (red ROI), fimbria of the hippocampus (yellow ROI), internal capsule (purple ROI), caudate putamen (green ROI). The corresponding Black-Gold-stained section is also shown.

Figure 2 shows the group FA values of the SHR and WKY at 10 and 40 weeks. In the corpus callosum, FA increased with age in both WKY and SHR. Corpus callosum FA was greater in SHR than in WKY, but the FA increase with age was smaller in 40 weeks old SHR, consistent with immunohistological measures of white matter density. Open field test showed that the 10 weeks old SHR had more significant hyperactivity than WKY and no significant different at 40 weeks old group.

In the fimbria of the hippocampus, FA was less in SHR than in WKY, consistent with immunohistological measures of white matter density. Water maze test showed that SHR performed worse cognitively than WKY in both age groups. FA of the internal capsule, caudate putamen, and anterior commissure (not shown) exhibited similar patterns as that of the fimbria of the hippocampus.

DISCUSSION and CONCLUSIONS: The major findings are: (1) Age-dependent increase in white matter density (by FA and Black-Gold stain) was smaller in SHR than WKY, suggestive of negative effects of hypertension. (2) Surprisingly, SHR FA was larger in SHR compared to WKY in the corpus callosum but the opposite was true in the fimbria of the hippocampus. We interpreted this finding as a characteristic of hyperactivity in SHR as observed (SHR is also used as a model of attention deficit hyperactivity disorder). Although this is a confounding factor, we concluded that white matter was reduced by hypertension as indicated by the weaker age-dependent increase in FA. (3) The FA of the fimbria of the hippocampus was lower in SHR compared to WKY, consistent with immunohistology. We interpret this finding as reduced white matter from the negative effects of chronic hypertension. This white-matter structure connects the hippocampus and is likely related to memory and we did find correlation with cognitive dysfunction in SHR. In conclusion, we found evidence of white-matter damage by chronic hypertension in an established animal model of hypertension, as observed by fractional anisotropy and immunohistology. These changes were manifested in the observed behavioral deficits associated regions connected by those white matter structures.