Temporal and spatial relation between vascular permeability and absolute brain water content in stroke-prone spontaneous hypertensive rats

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Introduction

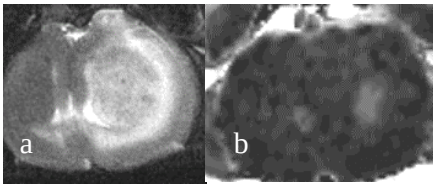
Stroke-prone spontaneous hypertensive rats (SHRsp) fed a high-salt, low-protein (Japanese-style) diet develop accelerated brain edema and spontaneous intracerebral hemorrhages. Although blood-brain-barrier (BBB) breakdown and cerebral edema have been well-described in this model, the spatial and temporal relationship between these two events has not been well-delineated. In the present study we serially imaged a cohort of SHRsp rats using MRI to examine vascular permeability and brain water content.

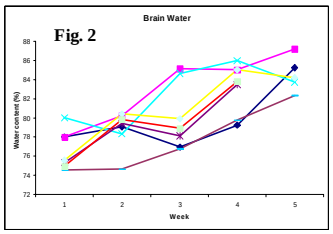
Methods

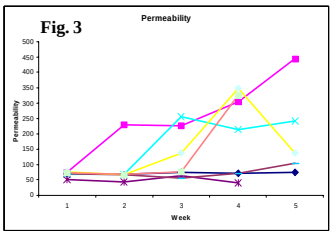
SHRsp rats (n=12), fed a high-salt low-protein diet after weaning, were imaged weekly on a 3T SIEMENS Allegra head-only scanner with a 4.3cm birdcage coil beginning at 12 week of age and continuing for five weeks. At each session, rats were anesthetized with isoflurane, and tail veins were catheterized for the injection of Gd-DTPA (0.15 cc/100 g) to facilitate permeability measurementIn order to obtain quantitative estimates of brain water content as well as to correct for T2* decay, a double echo 3D FLASH sequence was used to acquire images with five different flip angles, including 2°, 5°, 10°, 20°, and 40°. Imaging parameters were: TR = 35 ms, TE1 = 3.72 ms, TE2 = 15 ms, matrix size = 128 × 128, FOV = 32 mm^2 and 32 slices with a volume thickness of 32 mm. In addition, to further reduce transmitter miscalibration, a single echo 3D FLASH sequence was used with five large flip angles, including 160°, 170°, 180°, 190°, 200° and 210°. The imaging parameters for this sequence were identical to the 3D double echo sequence with the exception that only one echo (TE=3.72ms) was obtained. Furthermore, the spatial variations of the B1 were estimated using the square root of a set of images acquired using the 3D double echo FLASH with a flip angle of 2^0 and a homogeneous water phantom. Together, all of the above images were used to obtain quantitative measures of brain water content using our previously proposed approach (see ref xx for more details). A T2-weighted image was acquired using the following parameters: isotropic 32 cm field-of-view (FOV), 128x128 matrix size, 0.25 mm^3 pixel size, TR=6790ms, TE = 98 ms, and 30 slices. In order to obtain estimates of permeability, the Look-Locker (L-L) technique employing the T-one by multiple read-out pulses (TOMROP) sequence (ref1) was used for pixel-by-pixel estimates of T1. For the TOMROP sequence, a TI of 40 ms was used and a total of 20 and 9 echoes were acquired before and after the injection of contrast agent, respectively. Other imaging parameters were as follows: matrix size 128 × 64, FOV 32 mm and four 2 mm slices. The TOMROP sequence was repeated 10 times post-contrast. Finally, the PATLAK approach was utilized with the images acquired using the TOMROP sequence for obtaining permeability maps for each rat (ref1).

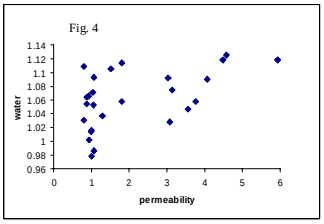
Regions of interest (ROIs) analysis was employed for the measurements of brain water content as well as vascular permeability for each rat at each time point. A ROI encompassing the T2 hyperintense lesion was used for brain water measurements across four adjacent slices and vascular permeability was recorded within the same ROIs.

Fig. 1









Results

All 12 rats developed asymmetric T2 hyperintensities by 14 weeks of age (Fig 1); 5 rats developed intracerebral hemorrhages at later time-points. Five rats died prematurely (before weeks 14) and thus were excluded from data analysis. In addition, the last time point was not available for two rats although results obtained from these two rats were included in data analysis. Representative T2-weigthed images and the permeability map from one rat is shown in Fig. 1. In addition, Fig. 2 and 3 show the temporal evolution of brain water content and vascular permeability over the 5-week observation period. Brain water content increases in all rats. In contrast, a minimal increase in permeability was observed in 3/7 rats while the remaining 4 exhibited substantial elevations in permeability. Finally, Fig. 4 shows the relation between normalized brain water content and permeability to that obtained at the first time point (week 12). As noted, the increase of permeability may not be a perquisite for edema formation while an increase of permeability is always associated with an elevation of brain water.

Discussion

The temporal and spatial relationship between permeability and water content suggests that cerebral edema may precede significant vascular injury in SHRsp rats. Increasing cerebral edema with time may subsequently lead to vascular injury and significant BBB breakdown (evidenced by late vascular permeability). In addition, severe BBB damage appears to occur focally, and may eventually result in frank intracerebral hemorrhage. By quantifying the evolution of vascular permeability and lesion formation, the progression of hypertensive cerebral pathology can be better understood.

References

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[2]R. Venkatesan, W. Lin et al. MRM, 2000;43(1):146-50.