DCE-MRI for Assessing Antiangiogenic Drug Effect in a Mouse with Choroidal Neovascularization

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Introduction

Age-related macular degeneration (ARMD) is the most common cause of visual loss and blindness (1, 2). Dry ARMD, also known as non-neovascular, may results from the aging and thinning of macular tissues, depositing of pigment in the macula, while wet ARMD, also known as neovascular, may be caused by choroidal neovascularization (CNV), a pathological process whereby abnormal new vessels arising from the choroidal capillaries grow though the membrane separating the choroid and the retina (Bruch's membrane). Recent developments in magnetic resonance imaging (MRI) have focused on quantitative measurement of functional change on monitoring therapeutic responses. Among MRI techniques, dynamic contrast-enhanced (DCE) MRI can provide functional information about vascular proliferation, and angiogenesis. Since vascular proliferation is an important factor to assess the treatment effect on CNV, we hypothesized that DCE-MRI can provide a non-invasive imaging biomarker to evaluate anti-angiogenic efficacy of macular degeneration.

Methods

Acquisition of MR Data: All MRI were carried out on a 7.0T MRI (Bruker-Biospin). The tail vein was cannulated for injection of contrast agent. DCE-MRI was performed using a coronal T_1-weighted 2D gradient echo sequence (FLASH sequence, TR=60 ms, TE=3 ms, flip angle=70°, resolution=200×200 μm^2, imaging matrix=128×128, slice thickness=1.0 mm, 120 dynamic images, time interval=6.0s). For T_1 mapping, five pre-contrast scans were acquired with the same post-contrast parameters, but only a different flip angle (5°, 15°, 35°, 60°, and 70°).

CNV mouse model: Mice were anesthetized with an intraperitoneal administration of avertin (240 mg/kg). A lesion was induced by a diode pumped solid state laser around the disc of the retina through a slit lamp delivery system using a photocoagulator.

Segmentation of retina: The retina in a mouse was automatically segmented on T2-weighted image. First, the inner surface of the eye was segmented using active contour method (3) for each eye. After segmentation of the inner surface of eye, the dilation operation was performed to expand the inner surface of eye using a disk mask with one-voxel radius. Finally, the retina was automatically segmented by subtraction of the inner surface eye from the dilated image.

Quantification of DCE image: The concentration of contrast agent in a tissue voxel was estimated using variable flip angle method (4). After converting MR signal intensity into concentration, the pharmacokinetic parameters were computed using the modified two compartment model. For statistical analysis, a paired Wilcoxon test was used to compare the measurements from pharmacokinetic parameters after 3 day, 7 day, and 14 day with those from base line.

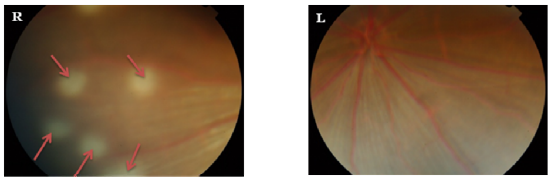

Fig. 1. Laser-induced CNV mouse model

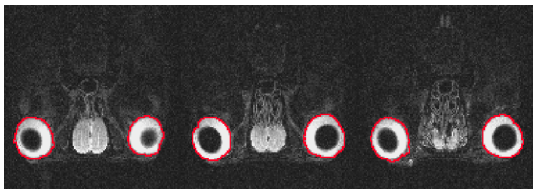

Fig. 2. Segmentation of retina using active contour method

Results

Fig. 1 showed autofluorescent for right and left maculas in a mouse at 3 days after surgical laser operation, and Fig. 2 showed the results of segmented retina in a mouse using active contour method. We found that the amplitude of the mean concentration profile from right retina was higher than that from left retina as a function of time in control group, whereas there were similar patterns of concentration between left and right retina in KR-31831 group at 7 and 14 days (Fig. 3). There were significant changes between control and KR-31831 group in K^{trans} ratio at 14 days ($P < 0.01$), whereas there were no significant changes in v_e, and v_p ratio at any time point.

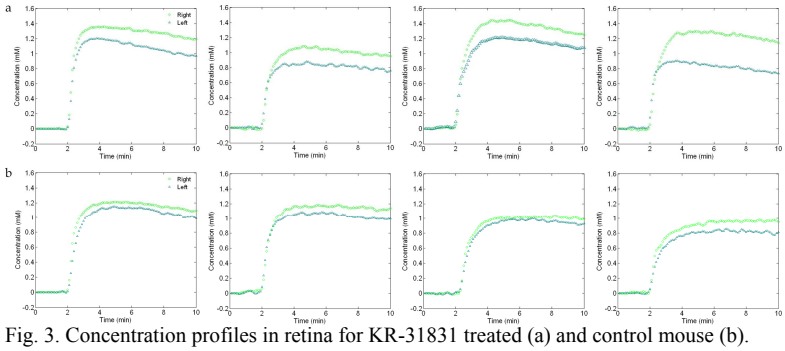

Fig. 3. Concentration profiles in retina for KR-31831 treated (a) and control mouse (b).

Discussion

KR-31831 is a newly developed small molecular weight drug as an anti-angiogenic candidate in our group.In previous animal experiments, our results showed that KR-31831 suppressed endothelial cell proliferation, tube formation, invasion, and migration in vitro and inhibited vessel formation in vivo (5). Moreover, our recent study demonstrated that KR-31831 has an anti-angiogenetic effect on xenografted human ovarian carcinoma mouse model in vivo. In this study, we also demonstrated that KR-31831 has an anti-angiogenetic effect on macular degeneration using a laser-induced CNV mouse model. In conclusion, DCE-MR imaging technique may be used as a noninvasive biomarker of choroidal neovascularization responsiveness to angiogenesis-inhibiting drug treatment.

References

1. Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA 2004; 291:1900-1901.
2. Ferris FL, et al. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol 1984; 102:1640-1642.
3. Chan TF, Vese LA. Active contours without edges. Ieee Transactions on Image Processing 2001; 10:266-277.
4. Fram EK, et al. Rapid calculation of T1 using variable flip angle gradient refocused imaging. Magn Reson Imaging 1987; 5:201-208.
5. Yi EY, et al. KR-31831, a new synthetic anti-ischemic agent, inhibits in vivo and in vitro angiogenesis. Exp Mol Med 2006; 38:502-508