Pharmacodynamic analysis of gadodiamide's diffusion through the focused-ultrasound blood-brain barrier opening in non-human primates in vivo using Magnetic Resonance Imaging

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Purpose

Focused Ultrasound (FUS) in conjunction with systemic administration of microbubbles has been previously shown to open the Blood-Brain Barrier (BBB) locally, non-invasively and reversibly on MRI in rodents[1]-[2] and non-human primates [3]-[5]. In rodents, physiological properties of the BBB opening, such as permeability, volume of reversibility timeline, have been studied [6],[7]; the purpose of this study was the investigation of the properties of BBB opening, including safety, in non-human primates (NHP). Pre- and post-contrast high resolution T1-weighted imaging, relaxometry imaging, T2-weighted and Susceptibility Weighted Imaging (SWI) was performed. Diffusion of gadodiamide into the brain parenchyma, which otherwise does not cross the BBB, was used as a tracer to depict the BBB-opened areas. Quantitative analysis of T1 and ΔR1 maps was performed to detect and quantify the volume of opening while contrast agent (CA) concentration maps were generated for pharmacodynamic analysis.

Methods

The putamen was targeted in two rhesus macaques using FUS (500 kHz center frequency; 5000 cycles pulse length; 2 Hz pulse repetition frequency; 60 s sonication duration, 300-400 kPa peak negative pressure) immediately after IV administration of monodisperse microbubbles ($8x10^5$/g) manufactured in house for transcranial BBB opening [10]. Following sonication, the macaques were placed in a 3T scanner (Philips Medical Systems, Andover, MA, USA). 3D T2-weighted imaging (Turbo Spin Echo, TR/TE = 3000/80 ms; flip angle (FA): 90°; NEX= 3; spatial resolution: 1 x 1 x 2 mm^3) and 3D SWI (TR/TE = 19/27 ms; flip angle: 15°; NEX= 1; spatial resolution: 1 x 1 x 1 mm^3) sequences were usedfor detection of hypointensity, e.g. hemorrhage, and hyperintensity, e.g. edema, respectively.

Five pre- and post-CA injection, 3D Spoiled Gradient Echo (SPGR) images (FOV:16 cm, matrix 160x160, TR/TE: 20/5ms, FA: 5° -55° , NEX=2, 1 x 1 x1 mm^3) were acquired and used for variable flip angle (VFA) based T1 relaxivity mapping, acquired before and after intravenous injection of gadodiamide (Gd-DTPA-BMA, 0.2 ml/kg). The BBB opening was detected by the increase in R1 as shown using ΔR1 maps. The volume of opening was quantified. Based upon the Bloch equation [11], a steady-state signal intensity (s_k) of a SPGR with a FA of a_k (k=1-5) and a TR is given by

$$s_k = M_o \sin(a_k)(1-E)/(1-E\cos(a_k)) \quad (1),$$

where M_o is the equilibrium longitudinal magnetization, and $E= e^{(-TR/T1)}$. Pre and post-contrast 3D SPGR images were processed off-line using an in-house algorithm developed in Matlab (MathWorks, Inc.). T1 and M_0 maps using the VFA method were generated by fitting the voxel-wise image intensities in Eq. (1) using non-linear least square fitting algorithm based on Levenberg-Marquardt algorithm. ΔR1 ($=R1_{post} - R1_{pre}$) maps were generated, and used for the detection and quantification of the BBB opening volume. The CA concentration (C_{Gd}) maps were then calculated from the $T_{1,pre}$ map before MR-CA injection and the $T_{1,post}$ maps after MR-CA injection using the following equation [12]: $[C_{Gd}] = \frac{1}{r_{Gd}}(\frac{1}{T_{1,post}} - \frac{1}{T_{1,pre}})$,where r_{Gd} is the relaxivity of gadodiamide equal to 2.6 mM^{-1}/s. Finally, the total C_{Gd} was measured over the entire volume of the BBB opening region.

Results

In the T1-w image shown in Figure 1, where the sonicated area is outlined with a dashed red region of interest (ROI), was not clearly depicted. However, the BBB-opened region is depicted by increased ΔR1 as shown in Figure 2. The voxels with higher ΔR1 within the sonicated area were included in the volume undergoing BBB opening while voxels with higher ΔR1 in the contralateral region were subtracted in order to exclude the effects of vasculature. Figure 3 shows the same coronal slice, overlaid with the C_{Gd} map, which reveals the increased CA concentration in the BBB opened areas. The total volume of opening was found to increase with pressure from 257 mm^3 to 483 mm^3, with an average C_{Gd} of 0.14 ± 0.05 mM / mm^3. In all cases studied, no edema (Fig. 4) or hemorrhage (Fig. 5) was detected.

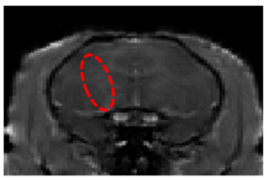

Fig. 1. CE-T1-w coronal slice. The ROI (sonicated area) is outlined with a dashed red ellipse. BBB opening is not clearly visible

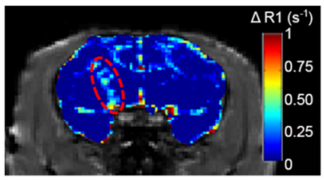

Fig. 2. T1-w coronal slice with overlaid ΔR1 map. The voxels with increased ΔR1 denote BBB opening in the ROI

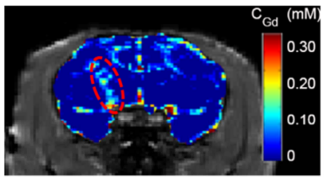

Fig. 3. T1-w coronal slice with overlaid ΔR1 map. The increased uptake in the ROI of opening is shown.

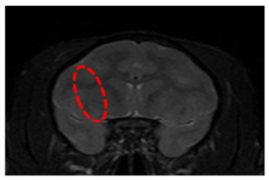

Fig. 4. T2-w TSE coronal slice

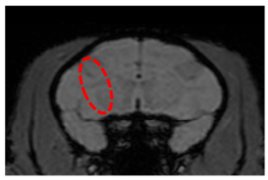

Fig. 5. SWI coronal slice

Discussion and Conclusion

In this study, physiological properties of the FUS-induced BBB opening in NHP, such as its volume and the concentration of gadodiamide perfusing the opened region, were quantified using T1 relaxivity and ΔR1 mapping in NHP in vivo for the first time, which was found to be more sensitive than standard T1 imaging (Fig. 1). The volume ranged within 257-483 mm^3 depending on the FUS pressure used while the concentration varied with an average of 0.14 ± 0.05 mM / mm^3. No associated edema or hemorrhage was detected within the FUS pressure range used. Monitoring of the volume and the CA concentration crossing the barrier opening could be used for assessment of the drug delivery as well as feedback control during BBB opening with FUS.

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