MONITORING ANGIOGENESIS IN NORMAL BRAIN USING STEADY-STATE QUANTIFICATION OF ΔR₂ (SSTAR2) WITH MION INFUSION

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INTRODUCTION

We have developed an MR imaging method (Steady-STATe quantification of ΔR₂ in tissue and blood with infusion of the stable contrast agent MION—SSTAR₂) in order to measure cerebral blood volume as a marker of angiogenesis. Angiogenesis is an important variable in conditions such as tumor growth and treatment, cardiac and cerebral ischemia, and chronic hypoxia. In this study, we apply our imaging method to a “natural” model of cerebral angiogenesis— that of chronic hypoxia exposure--to demonstrate that we can detect increases in cerebral blood volume over time in individual animals.

METHODS

MR imaging was conducted at 7T using a Varian console and a 4.5 cm quadrature birdcage coil. A multi-echo spin echo sequence was used to quantify R₂ \textit{in vivo} (TR=1.5 s, TE=0.011 s with 0.011 s inter-echo spacing, 14 echoes, FOV=3x3 cm, matrix=128x128, slice =1.5 mm, 4 transients). \textit{In vitro} calibration was done by adding MION (monocrystaline iron-oxide nanoparticles, 0-0.3 mg Fe/ml) [4] to rat serum, and imaging at 37°C using the same collection parameters. An \textit{in vivo} calibration was done by sequentially infusing MION intravenously for a total dose of 12 mg/kg. Multi-echo SE imaging \textit{in vivo} was done before and after infusion of 10 mg/kg MION. Blood samples were taken before and after the study in order to monitor hematocrit (Hct) and for the quantification of R₂. Serum R₂ values were measured using a 5-10 fold dilution of rat serum to quantify MION content at the same temperature, and with the same sequence as \textit{in vivo}. CBV was calculated as ΔR₂t/ΔR₂b, where Δ=the difference in R₂ before and after MION injection, t=cortical tissue, and b=blood. ΔR₂b was calculated as ΔR₂s · (1-Hct), where s=serum. The water exchange rate with erythrocytes is considered to be slow relative to the dephasing measured by T₂, and so red cell volume was added to the calculated serum volume to obtain a more accurate CBV [2, 3]. Angiogenesis was stimulated through exposure to ½ atm (hypoxia) for 28 days [1]. Imaging was repeated 1 day after the end of acclimation to reduce the potential for post-hypoxia hypercapnic increases in CBF.

RESULTS

Histologic studies demonstrate that the microvascular density was significantly increased post-acclimation (Fig. 1B, C, E). The capability of SSTAR₂ to monitor increased cerebral blood volume is shown in Fig 1D. Each individual animal studied showed a measurable increase in CBV as determined by MR quantification.

DISCUSSION and CONCLUSIONS

This study shows that SSTAR₂ can be used to monitor CBV as a marker of angiogenesis. The method has the potential for high resolution measurements, is quantifiable and can be repeated in the same animal over a time-course study.

REFERENCES