In vivo Targeted Drug Delivery to the Brain using MRI Guidance of Focused Ultrasound

L. H. Treat[1,2], N. McDannold[1], N. Vykhodtseva[1], Y. Zhang[1], K. Tam[1], K. Hynynen[1]

[1]Radiology, Harvard Medical School and Brigham & Women's Hospital, Boston, MA, United States, [2]Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA, United States

Introduction

The clinical application of chemotherapy to brain tumors has been severely limited because antitumor agents are typically unable to penetrate an intact blood-brain barrier (BBB). Nonlocalized diffuse opening of the BBB permits drugs to reach the brain but can have dose-limiting side effects. MRI-guided focused ultrasound (FUS) can be applied to the brain to temporarily disrupt the BBB in a targeted manner [1] and is thus an advantageous technique for drug delivery. In this study, we investigated the effect of FUS on the absorption of liposome-encapsulated doxorubicin in the rodent brain and the use of MRI to guide this procedure.

Methods

In a series of experiments, 35 male Sprague-Dawley rats (~0.4 kg) were anesthetized, shaved, and exposed to ultrasound focused at 4-mm depth in the brain, using a 1.7-MHz focused transducer. In each experiment, ultrasound contrast agent containing microbubbles was injected into the tail vein at the start of each sonication. Several different schemes of ultrasound exposure were explored. Liposome-encapsulated doxorubicin was administered following the microbubbles during sonication at various doses and delivery schedules.

A bolus of gadopentetate dimeglumine MR contrast agent (Magnevist; dose = 0.25 mL/kg) was injected into the tail vein after the last sonication. T1-weighted fast spin-echo (FSE) images were obtained on a 3-T clinical MRI scanner (GE Medical Systems) before and after the administration of the contrast agent to detect focal leakage of the contrast agent through the BBB. The difference in MR signal intensity at the focal location before and after the sonications was measured.

Trypan blue was administered to aid in the harvest of the sonicated and symmetric contralateral control tissue. Doxorubicin was extracted from sonicated and control tissue samples, quantified by fluorometry [2], and compared for statistical significance using a two-tailed paired Student's *t*-test. Several representative samples were obtained for histological evaluation.

Results

Tissue drug concentrations in sonicated brain were significantly different from those measured in symmetric unexposed control samples ($p = 0.01$). Tissue drug concentrations of 886 ± 327 ng/g tissue (mean ± SD) were achieved without significant tissue damage, while drug concentrations of up to 5366 ± 659 ng/g tissue were achieved with sonication parameters which also induced brain tissue lesions (data not shown). In addition, increased MR signal enhancement at the focal location on contrast-enhanced T1-weighted FSE images (Fig. 1) correlated with increased penetration of doxorubicin into brain tissue ($r = 0.85$) (Fig. 2).

Discussion

By applying focused ultrasound in the presence of microbubble ultrasound contrast agent, we achieved targeted drug delivery to the brain *in vivo*. Drug concentrations measured in sonicated brain tissue corresponded with cytotoxic levels measured *in vivo* in various human tumors [3]. Higher tissue drug concentrations were achieved at the expense of tissue damage, which may be acceptable to some extent in the context of tumor treatment. The correlation of MRI signal enhancement and drug absorption indicates the potential of MRI to be used as an indicator of BBB permeability during treatment.

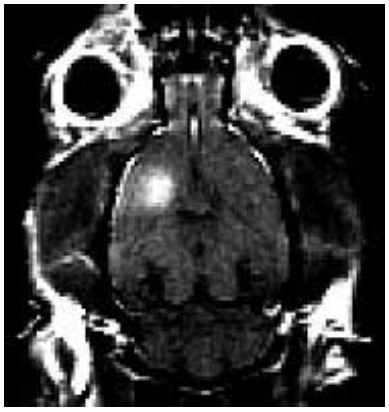

Fig. 1. T1w post-Gd FSE image showing localized penetration of contrast agent at focal ultrasound target in normal rodent brain.

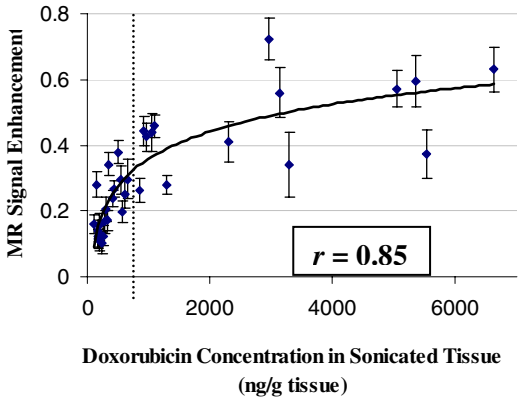

Fig. 2. Correlation of MRI and drug absorption in brain tissue. Dotted line indicates intra-tumoral drug concentration correlated with 39% patient response rate to doxorubicin for various human tumors [3].

References

1. Hynynen, K., *et al*. *Radiology* **220**, 640-646 (2001).
2. Bachur, N. R., *et al. Cancer Chemo Reports I* **54**, 89–94 (1970).
3. Cummings, J. & McArdle, C. S. *Br. J. Cancer* **53**, 835–838 (1986).

Acknowledgments

This research was supported by NIH grant EB003268, the Harvard-MIT Division of Health Sciences and Technology, and the MEMP Neuro-imaging Training Program (NIBIB grant 5T32EB001680).