Real time monitoring of hyperosmolar blood brain barrier disruption using MRI

M. Blanchette[1], M. Pellerin[2], L. Tremblay[2], D. Fortin[1], M. Lepage[2]

[1]Dept. of surgery, Université de Sherbrooke, Sherbrooke, QC, Canada, [2]Sherbrooke Molecular Imaging Centre, Université de Sherbrooke, Sherbrooke, QC, Canada

Introduction: Malignant astrocytomas are aggressive primary brain lesions with a dismal prognosis. Because of their infiltrative behavior, these tumors are invariably incurable by surgery. Radiotherapy is of limited benefit, with an extension of survival averaging 6 months. Chemotherapy has also been of limited benefit, because of two factors: the intrinsic chemoresistance of tumor cells and the impediment in delivery caused by the blood brain barrier (BBB). The normal BBB blocks ionized water-soluble compounds with a molecular weight greater than 180 Daltons. Different approaches have been advocated to improve delivery across the BBB. One such strategy is the osmotic opening of the BBB (BBBD)[1]. It involves the cerebral intravascular infusion of hypertonic solutions to produce a transient increase in permeabilization of the barrier, in a given cerebral distribution (carotid or vertebral). There is now extensive animal and human clinical data on the use of this approach.[2] Nonetheless, the exact process and physiology of the procedure have not been detailed. This study was initiated with the goal of characterizing spatially and temporally the BBBD procedure with MRI.

Methods: A technique was devised so the BBBD procedure could be accomplished while the animal was positioned on its back in a 7 Teslas (Varian, Palo Alto, USA) animal scanner. Thus, images were acquired before, during and after the BBBD procedure. Osmotic BBBD was performed in 24 healthy Wistar rats by the infusion of mannitol 25% in the right external carotid artery with an infusion rate of 0.12 cc/s for 30 seconds. All animals were under general anesthesia (propofol and isoflurane 1%). At a selected time after BBBD, a bolus of 500 µl, 3:1 Gd-DTPA was injected i.v. (tail vein). T_1-weighted images (TR/TE: 100/2.4 ms, FOV: 4 x 4 cm^2, matrix: (128)^2, α: 30°, NA: 4) were acquired 2 minutes prior to the BBBD procedure, and periodically following the procedure, up to 2 hours.

Results: Mathematical analysis of the signal enhancement patterns was performed to extract the rate of perfusion and the amplitude of signal enhancement (Fig. 1). While this is small compared to muscle tissue, we observed a 3-fold signal increase in the brain parenchyma in the treated hemisphere (yellow arrow) compared to the contralateral hemisphere (cyan arrow), which remained at, or slightly higher than, background level (Fig. 2). In the region of the basal nuclei (white arrow) a 5-fold enhancement when compared with the untreated hemisphere was observed in some animals. Interestingly, the Gd-DTPA remained in the brain parenchyma longer than anticipated (> 2 h).

Conclusion and perspectives: These results demonstrate the efficacy of the procedure to increase the BBB permeability that allows the accumulation of a small molecule (Gd-DTPA) in the brain parenchyma. Further experiments will use larger molecular weight compounds and tumor-bearing rats. The results have a direct impact in clinic, as the time of exposure of the tumor cell to a chemotherapeutic agent, as well as the effective concentration of the agent beyond the BBB, are important surrogates in oncology.

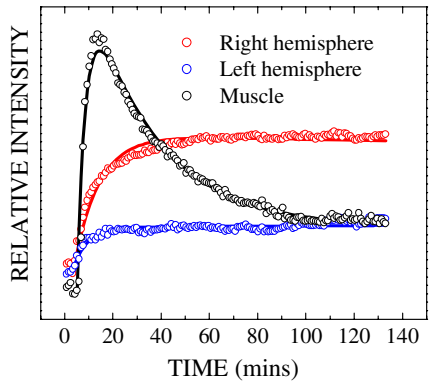

Figure 1. Signal intensity for different regions of the brain and for muscle tissue (open dots) following BBBD and injection of Gd-DTPA. While the intensity in muscle reaches a maximum within 20 minutes, it decreases sharply thereafter. In contrast, the intensity in the brain hemispheres remains constant with a higher intensity in the hemisphere opened by BBBD. Fits are also shown (solid lines).

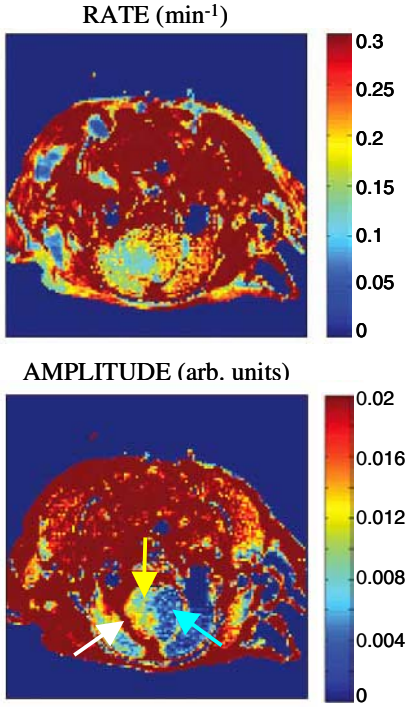

Figure 2. Axial brain maps for the rate and the amplitude of Gd-DTPA perfusion injected two minutes after BBBD. BBBD of the right hemisphere (left on figure) results in a significant accumulation of Gd-DTPA. The signal enhancement persisted for over 2 hours.

References: **1-** D. Fortin (2003), Peptide transport and delivery to the CNS. Progress in drug research, Prokai L, Prokai-Tatrai K eds., vol 61. p 127-154, Birkhauser, Switzerland. **2-** D. J. Kraemer, D. Fortin, E. A. Neuwelt, Current Neurology and Neurosciences Reports 2:216-224, 2002.