Dynamic diffusion process of MRI contrast agents into the brain following blood-brain barrier disruption

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

[1]Centre d'imagerie moléculaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, Canada, [2]Dép. de chirurgie, Université de Sherbrooke, Sherbrooke, QC, Canada

Introduction : Chemotherapy treatment of malignant astrocytomas is limited by two factors. First, the natural or acquired resistance to chemotherapy expressed by tumor cells and poor penetration of antineoplasic agents into the central nervous system (CNS) due to the blood-brain barrier (BBB). The BBB normally blocks the diffusion of ionized water-soluble molecules with a molecular weight greater than 120 Da. Different strategies have been developed to improve delivery across the BBB. One of them is the osmotic blood-brain barrier disruption (BBBD). This approach involves a cerebral intra-arterial infusion of a hyperosmolar solution to produce a temporary permeabilization of the BBB in a given cerebral distribution pathway (carotid or vertebral). The efficacy and safety of the procedure have been demonstrated in the clinic.[1] Here, we report on the transport mechanism of an agent within the brain after BBBD and on the quantification of the exposure of the brain tissue to an agent.

Methods : The BBBD procedure was performed on animals positioned on their back in a 7T animal scanner (Varian, Palo Alto, USA). Images were acquired dynamically before, during and after BBBD. Osmotic BBBD in healthy Wistar rats was achieved by the infusion of mannitol 25% in the right external carotid artery with an infusion rate of 0.12 cc/s or 0.14 cc/s for 30 seconds. All animals were under general anaesthesia (propofol and isoflurane 1% when required). A time delay of 1, 2, 3, 5, 10, 15, 20, or 30 min was inserted between the BBBD and a bolus injection of 500 µl, 3:1 Gd-DTPA (n=47) or Gadomer (n=9) injected i.v. via the 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, for up to 2 h. A pre-contrast T_1 map was calculated from images recorded using the same parameters and α: [10°, 20°, 25°, 35°, 50°]. Thus, a signal enhancement could be calibrated in terms of the concentration of an agent using the same formalism as regular DCE-MRI studies.[2]

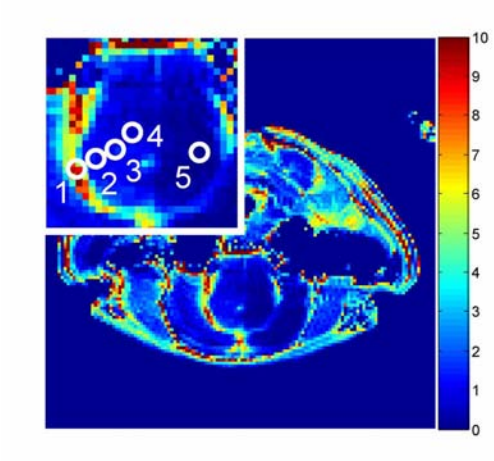

Fig. 1. Exposure of the brain (in mM*min) to Gd-DTPA injected three minutes after BBBD.

Results : We calibrated the signal enhancement time curve for each pixel in a series of images in terms of the concentration of agent. Those results are expressed as "exposure" maps, which represent the pixel-by-pixel integral of the concentration of the agent over time (in mM*min). Fig. 1 displays the exposure of a healthy brain to Gd-DTPA for the first 17 minutes when injected 3 minutes after BBBD. Different regions of the brain have a different exposure to Gd-DTPA, highlighting the heterogeneous nature of the penetration and transport of an agent into the CNS after BBBD. The time curves for the ROIs indicated on Fig. 1 are shown on Fig. 2. The maximum concentration is reached at a time which depends on the distance from a well perfused region (Fig. 1, ROI 1) between the cortex and the striatum in the treated hemisphere. This suggests two mechanisms are at play. First, direct permeabilization of the BBB accounts for the initial signal rise. Then, diffusion of the agent within the brain is responsible for a delayed, broader distribution of Gd-DTPA in ROIs 2 to 4. This fact is highlighted for ROI 5, which is located in the contralateral hemisphere and which reaches a maximum concentration at around 67 min. The therapeutic window, which we define as the exposure as a function of the delay between BBBD and injection of a contrast agent, displays a maximum at approximately 3 minutes after BBBD. The same phenomena (direct permeabilization and diffusion) were observed from measurements using Gadomer. Moreover, the exposure did not differ dramatically when one or the other agent was used. This was surprising considering the very different molecular weights of Gd-DTPA (0.9 kDa) and Gadomer (17 kDa). However, the exposure did increase significantly for both agents when a higher infusion rate of mannitol was used.

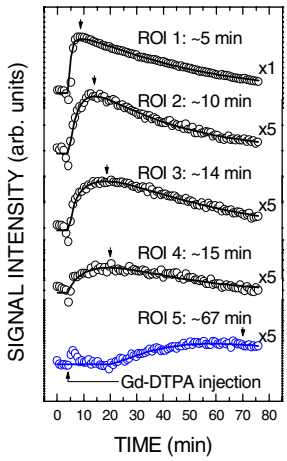

Fig. 2. Sgnal enhancement time curves for the ROIs indicated in Fig. 1. The time to reach maximum after injection is indicated by arrows.

Conclusion : The results show that BBBD is an efficient technique to enhance the delivery of molecules with different molecular weights to the CNS. Two different mechanisms are responsible for the delivery of agents to the CNS. First, direct permeabilization of the BBB and second, diffusion of an agent within the brain tissue both appear to contribute to the exposure. Maximum exposure is achieved when the injection is made 3 minutes after BBBD, regardless of the mannitol infusion rate.

References : **1-** Doolittle N *et al*. Cancer 88, 637-47 (2000). **2-** Yankeelov *et al.* Magn. Reson. Imaging 23, 519-529 (2005).