MRI assessment of bradykinin B2 receptor-mediated selective blood-brain barrier disruption in a F98 glioma rat model

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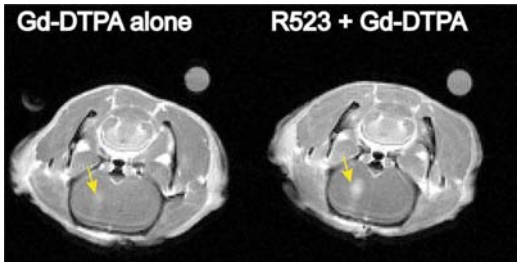
Introduction: There is now convincing evidence suggesting that B2 receptor activation by bradykinin (BK) mediates selective blood-brain barrier disruption (BBBD) of tumors, including gliomas, the most prevalent type of brain tumors.[1] Herein, MRI with intravenous Gd-DTPA was used to monitor and validate the increased blood-brain tumor barrier (BBTB) permeability induced by a stable synthetic B2 receptor agonist [Phe$^8\psi$(CH_2NH)Arg^9]-bradykinin (R523) in F98 glioma-implanted Fischer rats.[2,3] We hypothesized that an effective permeabilization of the BBTB would increase the apparent cerebral tumor volume (ACTV) on post-contrast T_1-weighted images.

Methods: Adult male Fischer rats were implanted with 1x10^4 F98 glioma cells (5 μl) in their right hemisphere using a stereotactic frame. All experiments were performed on anesthetized animals (isoflurane 1%) placed in dorsal decubitus position in a 7T animal MRI (Varian, Palo Alto, USA). T_1-weighted images (TR/TE: 100/2.4 ms, FOV: 4 x 4 cm^2, matrix: (128)^2, α: 30°, NA: 4, 10 slices of 1.5 mm) were repeatedly acquired for a time period of 40 min before, during and after i.v. (tail vein) injection of a bolus of Gd-DTPA (500 μl). Ten days after implantation, a baseline measurement was recorded for each animal after the injection of Gd-DTPA alone. Four hours later, the vehicle solution alone (isotonic saline, control experiment) or the solution of R523 (10 nmol/kg, BBBD procedure) was infused in the right external carotid artery (0.1 ml/min for 5 min) followed immediately by the bolus of Gd-DTPA. These were performed in the presence or absence of the potent B2 antagonist HOE-140 (20 nmol/kg). A pixel-by-pixel analysis of the signal in the series of images identified the pixels where the signal exceeded a threshold, which was set by a histogram analysis of the 10-min post-contrast image. The ACTV was calculated by adding the volume of voxels with intensity higher than a second threshold, and by adding a partial volume proportional to the signal enhancement for the voxels whose intensity lied between the two thresholds.

Results: Our results showed that the ACTV of a rat glioma nearly doubled from the baseline value after an intracarotid infusion of R523 (Fig. 1). The intensity of the normal brain parenchyma from the ipsi and contralateral hemispheres remained at baseline. The maximum ACTV ranged from 20 mm^3 in the control experiment (Gd alone) to 36 mm^3 in the agonist-treated animals. This increase in ACTV was not detected in the control experiment (vehicle alone) and was negated by co-infusion of excess cognate antagonist HOE-140 (not shown), thus confirming that the effect of R523 is *via* a receptor-mediated mechanism.

Conclusion & perspectives: Our results support the notion that BK agonists can be used as BBTB permeabilizers and that MRI can be used to monitor this effect. At the moment, it is not clear whether the R523-evoked Gd-DTPA signal enhancement within the brain tumor reflects genuine increased levels of extravasated Gd-DTPA rather than regional hemodynamic disturbance (e.g. hyperemia) occurring at the tumor vascular network. Notwithstanding this uncertainty, we conclude that MRI offers a promising approach, which can also be applied in a clinical setting, to follow non-invasively the dynamic evolution of BBTB induced by pharmacological agents. A chemotherapeutic agent co-infused with R523 is expected to reach more effectively the poorly vascularized regions of a tumor, as well as regions around a tumor where a few cells may have infiltrated the normal brain tissue, thus possibly enhancing the efficacy of that agent. Finally, alternative delivery modes should be tested to increase the clinical usefulness of BK agonists.



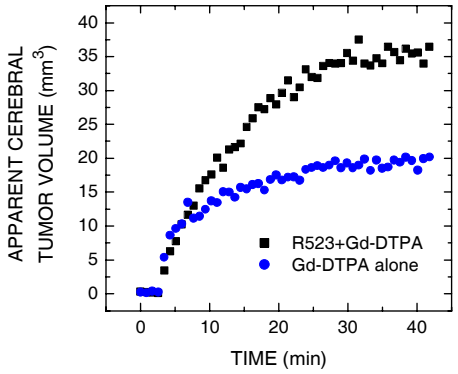


Fig.1. Representative Gd-DTPA enhanced images of a tumor-bearing rat prior (upper left) and after (upper right) BBTB in the right hemisphere. Tumor localization is indicated by arrows. Calibration samples are seen at the top right of each image. ACTV calculated from the corresponding set of images (bottom panel).

References: (1) Rapoport SI, Cell. Mol. Neurobiol. 20 : 217-230, 2000. (2) Drapeau G *et al*, Eur. J. Pharmacol. 155 : 193-195, 1988. (3) Mathieu D *et al*, J. Appl. Res. 5 : 1-17, 2005.