Selective blood-brain barrier permeabilization of F98 rat glioma to a high molecular weight contrast agent by an inducible kinin B1 receptor agonist

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Introduction: Treatment of brain tumors with chemotherapy is limited mostly because the blood-brain barrier (BBB) prevents the delivery of drugs to migrating tumor cells. Multiple techniques have been studied to improve delivery across the BBB (e.g., mannitol intra-carotid infusion and focused ultrasound). Recent evidence suggests that vascular kinin B1 receptors (B1R), a protein whose expression is only induced in a pathological context (e.g., tumors), can regulate BBB permeability, including that of brain tumors. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) with intravenous Gd-DTPA (0.5 kDa) or Gadomer (17 kDa) was used to monitor and validate the selective increase of BBB permeability at the tumor of F98 glioma-bearing Fischer rats, induced by either the natural B1R agonist (LDBK) or NG29, a synthetic high-affinity B1R agonist. We hypothesized that an effective permeabilization at the tumor and its periphery would increase both contrast agents distribution volume and the total concentration into the tumor-bearing hemisphere of the brain.

Methods: Glioma cells were inoculated stereotactically into the right caudate nucleus in a total of 75 Fischer rats. After ten days, MRI experiments were conducted on anesthetized animals placed in a 7T animal MRI scanner. A pre-contrast T_1 map was acquired using T_1-weighted images with different flip angles (TR/TE: 100/2.4 ms, FOV: 4 x 4 cm^2, matrix: (128)^2, α: [10-50°], NA: 4, 10 slices of 1.5 mm). A bolus of either Gd-DTPA or a larger Gd-based contrast agent (Gadomer) was injected via the tail vein with simultaneous and continuous monitoring by T_1-weighted images (α: 30° for a time period of 30 min. This allowed the evaluation of the extent of the basal BBB permeability at the tumor and served as the reference volume and concentration. Twelve hours later, a B1R agonist (0.1 ml/min for 5 min; 2.5, 10 or 50 nmol/kg/min) was infused in the right external carotid artery leading directly to the tumor-bearing hemisphere and the same MRI experiments were repeated. The concentration of contrast agent was calculated for every image in the dynamic series. In addition, a contrast agent distribution volume (CADV) was calculated based on a threshold analysis. Since the normal BBB prevents the delivery of both contrast agents, the CADV reflects the volume where the BBB is leaky or has been permeabilized. Blood samples were collected at different time points following Gd-DTPA injection (1, 3, 5, 15, 30, 60, 120 min), centrifuged to isolate plasma, and analysed with inductively coupled plasma mass spectroscopy (ICP-MS) to obtain the plasma Gd concentration and create time-elimination curves.

Results: Our results suggest that the intracarotid infusion of NG29, but not LDBK, modulates topographic uptake profiles of both contrast agents within rat glioma and brain tissue surrounding the tumor, as observed by increase of both CADV and mean Gd concentration in the implanted hemisphere (fig. A-D). The latter effect was not seen in normal brain parenchyma from ipsi and contralateral hemispheres (fig. D), and was negated by co-infusion of excess B1R antagonist R892 or cyclo-oxygenase inhibitor meclofenamate, but not by B2R antagonist HOE140 or by nitric oxide synthase inhibitor L-NA. The BBB permeabilizing effect of NG29 lasted less than two hours and did not affect blood pressure; neither did it influence the contrast agent elimination from the blood, as demonstrated by ICP-MS.

Conclusion: We conclude that MRI offers a promising approach to monitor non-invasively the dynamic evolution of BBB permeabilization locally induced by the B1R agonist NG29. Since expression of B1R is confined to the tumor vasculature and its periphery, we suggest that a chemotherapeutic agent co-infused with NG29 will reach more efficiently the poorly vascularized regions of a tumor, as well as regions around the tumor where glioma cells have infiltrated, thus possibly enhancing the efficacy of that cytotoxic agent, while limiting undesired effects.

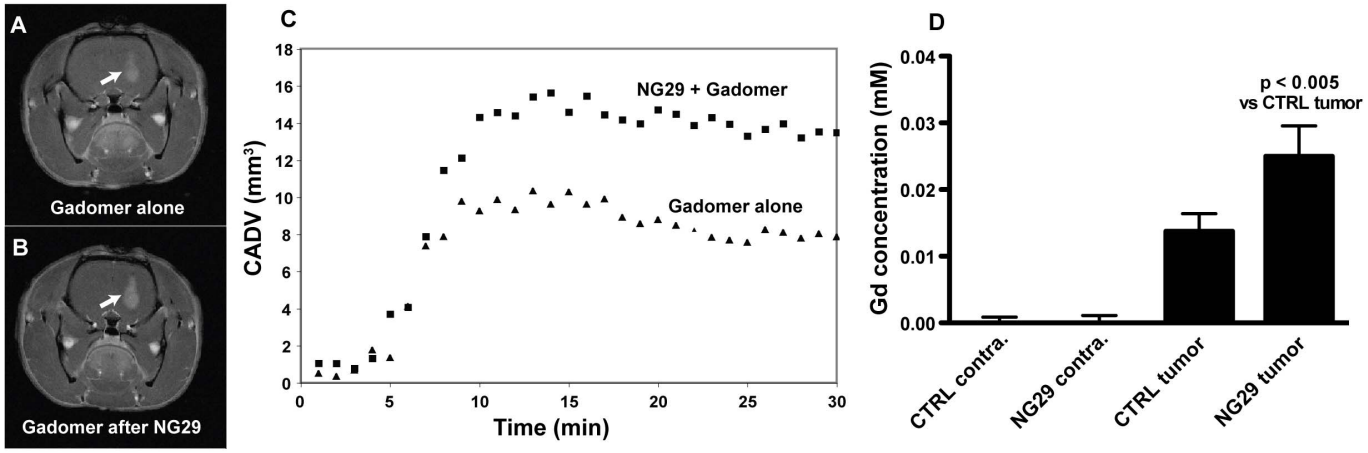

Figure 1 – NG29-mediated BBB disruption in F98 glioma-bearing rats assessed by MRI using Gadomer. (A) and (B) Representative axial Gadomer-enhanced T_1-weighted MR images depicting the brain of an F98-implanted rat before and after treatment with NG29. Note the increase of the signal intensity and volume of distribution at the tumor (white arrows). (C) CADV calculated from the corresponding set of images (1 image / 51 s). (D) Mean Gadomer concentration calculated from the same set of images, using regions of interest corresponding to either the implanted (tumor) or non-implanted (contra.) hemisphere of the brain, before or after treatment with NG29.