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(G*) Cariporide Effects on Intracellular pH (pHi) Using CEST-MRI in Rat Model of Glioblastoma

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Introduction: pHi is a hallmark of altered cellular function in the tumour microenvironment and its response to therapies. One of the main acid-extruding membrane transport proteins in cells is the Na+/H+ exchanger isoform 1 (NHE1). Chemical exchange saturation transfer (CEST) MRI uniquely images pHi. In CEST-MRI, contrast is produced by exciting exchangeable tissue protons at their specific absorption frequency and observing the transfer of magnetization to bulk tissue water. Amine and amide concentration-independent detection (AACID) is a ratiometric approach that uses the distinctive sensitivity of amine and amide protons to CETS contrast. The AACID value inversely relates to tissue pHi. One way to achieve tumour acidification as a therapeutic strategy is by blocking the NHE1 transporter. Cariporide is a potent inhibitor of NHE1. We have shown that cariporide can selectively acidify U87MG glioma in mice. The goal of this study was to determine whether cariporide also selectively acidifies a rat C6 glioma tumour model immediately following injection by mapping tumour pHi.
Methods: A 2μL suspension of 10ˆ6 C6 glioma cells were injected into the right frontal lobe of six 8-week-old male rats. To evaluate the effect of cariporide on tumour pHi, rats received an IP injection of the drug (6mg/kg in 2ml) two weeks after tumour implantation. They received the drug inside a 9.4T scanner to measure the change in pHi following injection.
Results: Five minutes after injection we started collecting CEST-MRI for 3 hours. For data analysis, we compared the first maximum change in AACID value post-injection with the pre-injection value. Approximately 60 minutes after injection, the average AACID value in the tumour significantly increased ($p<0.05$). The average AACID value in tumour post-injection was 5.4% higher compared to pre-injection corresponding to a 0.26 lower pHi. The average AACID value in contralateral tissue also increased in a similar way.
Conclusion: We did not observe selective tumour acidification following injection as was observed in the previous study. The reason for this discrepancy is currently unknown but may be related to potential differences in tumour vasculature that may limit the ability of cariporide to infiltrate the tumour. Future work includes increasing cariporide dose and modifying our quantification method to increase the temporal stability of the AACID measurement.

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