Selective acidification of tumour extracellular pH using glucose measured by Amide Proton Transfer MRI

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Introduction

Amide Proton Transfer (APT) MRI signals are sensitive to tissue pH by virtue of the base-catalysed exchange rate of amide and water protons[1]. However, the extent to which intra- and extracellular tumour pH changes contribute to altered APT MRI signals in tumours remains to be elucidated. The APT signal is assumed to predominantly originate from the intracellular compartment, while possible extracellular contributions are widely ignored[1,2,3]. Selective acidification of the extracellular space of tumours following glucose administration has been observed previously[4]. Here, the influence of selective acidification of the tumour microenvironment induced by glucose injection on APT MRI signals is assessed.

Methods

Female Berlin-Druckrey IX rats (n=6) injected intracerebrally with ENU1564 cells were used as a model of breast cancer brain metastasis. MRI was performed using a 9.4 T spectrometer. Baseline blood sampling from a femoral artery and APT MRI (2 s pulsed saturation, equivalent continuous power 0.55 μT, 34 saturation frequencies between ±300 ppm relative to water) were performed before intraperitoneal injection of 6 g/kg glucose. APT MRI and simultaneous blood sampling were repeated every 16 minutes over a total imaging time of 2.5h. Blood glucose levels were determined using the PGO Enzyme Preparation Assay. The APT effect was quantified in tumour and contralateral regions of interest by the APTR* metric[5], which is sensitive only to changes in pH and protein concentration[6] using Quantiphyse[7]. Relative APTR* values were obtained by normalisation of tumour APTR* to contralateral APTR*.

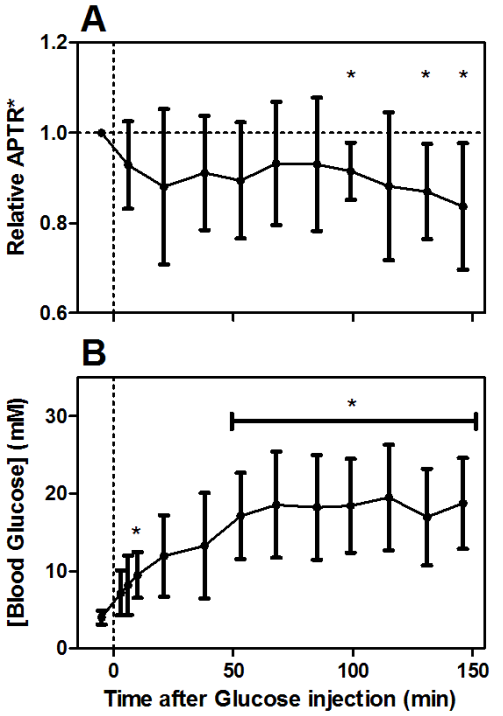

Figure 1: Changes in Relative APTR* (A), and Blood Glucose Concentration (B), over time after Glucose injection. 95% Confidence Intervals shown.

Results

Relative APTR* decreased significantly to 84 ± 14 % (Mean ± 95% CI) of pre-glucose injection levels after 2.5h (Fig 1A). Blood glucose concentration increased significantly from 4.0 ± 0.9 mM at baseline to 17.1 ± 5.6 mM after 60 min, but did not change significantly from this time until the end of imaging (Fig 1B).

Discussion and Conclusion

The measured increase in blood glucose concentration is in agreement with previous studies that have used similar glucose doses to induce tumour extracellular acidification of 0.5 pH units[8]. Assuming a stable protein concentration throughout the experiment, the results of this study show that APT MRI is sensitive to selective acidification of the extracellular environment of tumours, suggesting that there is a clear contribution of extracellular amide protons to APTR* signals.

References

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