Noninvasive characterisation of a rat model of brain metastasis using MP-pCASL and APT MRI

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Introduction

Arterial spin labelling (ASL) MRI has numerous potential applications in the clinic as a non-invasive method to measure perfusion in the brain. We have previously determined optimised parameters for ASL in rats by using a multiphase pseudo-continuous ASL (MP-pCASL)[1]. Alternatively, amide proton transfer (APT) MRI, is thought to be sensitive to changes in intracellular pH and protein content[2]. Here, our aim was to demonstrate the sensitivity of MP-pCASL and APT MRI to changes in tumour perfusion and pH, respectively, in a rat model of brain metastasis.

Methods

Female Berlin-Druckrey IX (BD-IX) rats were injected in the left striatum with 1000 ENU1564 cells. MRI experiments were performed on isoflurane anaesthetised rats at weeks 2, 3, and 4 post-injection using a 9.4 T MRI spectrometer. Pre- and post-gadolinium T_1- and T_2-weighted images were acquired for each animal. Additionally, MP-pCASL data were acquired using a 6.2 mm wide tagging plane with a labelling bolus duration of 1.4 s and post-label delay (PLD) of 0.65 s, based on multi-PLD MP-pCASL arrival maps (TR=4 s, TE=28.7 ms). MP-pCASL[3] used radiofrequency (RF) pulses with eight phase angles between 0˚ and 315˚. Data were analysed using a modified version of BASIL[4] to obtain cerebral blood flow (CBF) maps. APT-MRI was acquired using a 2 s pulsed saturation (equivalent continuous wave power 0.55μT) for 51 saturation frequencies, and was quantified using the APTR* metric[5] in Quantiphyse[6]. Following MRI, rat brains were sectioned using a cryostat and immunohistochemistry was performed looking at hypoxia (pimonidazole), vessels (CD31), angiogenesis (Tie2), and protein (Coomassie).

Results

Metastatic tumours were visible on T_2-weighted images of metastasis-bearing rats from 2 weeks post-injection. Blood-brain barrier breakdown occurred between weeks 2 and 3, as demonstrated by hyperintense regions on post-gadolinium T_1-weighted images. At this time, MP-pCASL showed a significant decrease in CBF within the tumour compared to the contralateral striatum ($p < 0.01$). The tumour core showed the greatest reduction in CBF and histologically was found to be hypoxic in regions distant to blood vessels. By week 4, protein concentration assessed histologically was significantly increased in the tumour rim ($p < 0.05$) and significantly decreased in the tumour core ($p < 0.001$) compared to the contralateral striatum. Taking protein concentration changes into account, the intracellular pH of the tumour rim was found to have increased to 7.14 ± 0.01, compared to an assumed pH of 7.10 in the contralateral control striatum, as determined by APT-MRI.

Discussion and Conclusion

The significant decrease in tumour perfusion is indicative of dysregulated blood flow within the tumour. The elevated presence of pimonidazole staining in areas further from vessels within brain metastases provides evidence of hypoxia within these tumours, a consequence of reduced blood flow in these areas. The presence of hypoxia suggests that these tumours would be poor responders to radiation therapy. The increase in intracellular tumour pH at later time points, is consistent with studies in other tumour types[7], and indicates that APT MRI is sensitive to changes in tumour pH. We propose, therefore, that MP-pCASL and APT MRI may be useful tools in treatment planning for brain metastasis.

References

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