Integrated MR and EPR imaging for evaluating tissue oxygenation and oxidative stress in stroke

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Abstract

Imaging has emerged as an important tool for investigative research in the field of Neurology and Neuroscience. Imaging modalities such as MRI, EPR, micro-PET and micro-CT allow live animal imaging that is useful for performing longitudinal studies without the need to sacrifice animals. In this study we have demonstrated the role of MR and EPR integrated imaging for studying focal cerebral ischemia in a mouse model. Whereas EPR produced functional maps of the ischemic lesion, MRI provided complimentary anatomical information of the ischemic lesion. At UNM, the new BRAIN center houses 4 imaging modalities under one roof that has made integrated imaging feasible and practical for neuroscience research.

Introduction

Stroke is the third leading cause of mortality and morbidity in humans and ischemia accounts for approximately 80% of all strokes. In ischemic stroke, there is a decrease in the partial pressure of oxygen (pO_2) in the ischemic zone due to occluded vascular territory, which is most likely due a combination of reduced O_2-delivery and increased O_2-extraction. Higher O_2-extraction rate is probably due to increased metabolic demands to prevent tissue damage. An understanding of change in O2 delivery and extraction in the region of stroke due to modified Cerebral Blood Flow (CBF) is very useful for developing newer stroke treatment modalities. EPR (Electron paramagnetic resonance) imaging is a relatively new method for interstitial pO_2 measurement in living animals and mapping CBF (1). EPR measures the molecules with an unpaired electron, i.e., free radicals or paramagnetic species. By using the appropriate stable imaging agent (to increase sensitivity), EPR can provide important information about tissue oxygenation and oxidative stress. At the usual frequency of 0.5-1.2 GHz for in vivo EPR, a depth of penetration of up to 30 mm is achievable, which is sufficient for imaging small animals, such as mice and rats. Unfortunately, EPRI generates poor soft tissue contrast, however when integrated with MRI (for excellent structural information) may prove to be a powerful tool to investigate cerebral ischemia. In the present study, we demonstrate the role of integrated MRI and EPRI of the brain of mice undergoing focal ischemia.

Materials and Methods

An MCAO in a male c57 mouse model was performed for 60 minutes using a modified intraluminal method to create an ischemic stroke lesion in the right cerebral hemisphere. MR imaging of mouse was performed 48 hrs post MCAO on a 4.0T Siemens whole body clinical scanner using a quadrature volume RF coil (INSL, Boston) with I.D. 72mm. Isoflurane was used as a maintenance anesthetic while the mouse was positioned and imaged in the scanner. The total duration of the study was approximately 1 hour, which included experiment setup time. Real time monitoring of physiological parameters (heart rate and O2 saturation) was performed during the entire duration of the study. T2 weighted images were acquired (post localizer) using the following parameters: 2D Multi shot RARE (Rapid Acquisition with Relaxation Enhancement), coronal plane , TR/eff_TE 4.5s/72ms, matrix 256x128, FOV 25mm x 25mm, slice thickness/slice gap 3.0/0mm , number of signal averages 32, ETL 5. Prior to EPR imaging acetoxymethyl ester of 3-carboxy-2,2,5,5-tetramethyl-1-pyrrolidinyloxy (AM-CTP, 100 mM, 0.5 ml), a paramagnetic imaging agent, was intraperitoneally administered to the mouse 15 min after MCAO and imaged using EPR (post MR imaging) by placing mouse in the cavity of a new Bruker L-band EPR E540 image system equipped with BLGR (Piezo) resonator and a L-band bridge. For the recording of the 3D image data, following EPR parameters were used in the experiments: 1.1 GHz microwave at a power of 18 mW, 100 kHz field modulation of 0.1 mT, external magnetic field of 39 ± 5 mT. The EPR image of ischemic brain was reconstructed with back projection method using Bruker Xepr software.

Results

Images acquired using EPR and MR technique are shown in the figure below. T2 weighted MR image very well demonstrates the stroke lesion in the right cerebral hemisphere. The EPR image obtained from the ischemic brain shows two important features. First, due to the reduced blood flow to the ischemic region, the concentration of the imaging agent in the ischemic region is dramatically reduced, as compared to the non-ischemic tissue. Second, the blood flow to the ischemic core is known to be reduced close to zero, therefore, on the EPR image, no EPR signal was observable in the ischemic core, thus defining the region of ischemic core. On the T2w MRI image of the same animal, the ischemic core is shown as hyperintense, confirming the EPR finding.

Discussion

In this study role of integrative EPR and MR imaging has been demonstrated in focal ischemic mouse model. EPR imaging provides high resolution functional maps of ischemic brain lesion after injection of a paramagnetic agent. The anatomical information of the lesion is provided by T2w MR Image. At UNM, the new BRAIN center will house imaging modalities (such as MRI, EPR, MEG, Photon microscopy under one roof) that will make integrative imaging practical and useful for neuroscience research.

References

1. Swartz, H.M. (2002) Measuring real levels of oxygen in vivo: opportunities and challenges. *Biochem. Soc. Trans.*, **30**, 248-52

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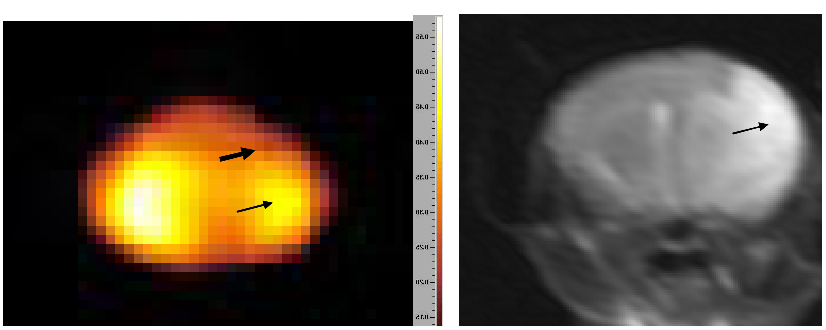

Figure shows an EPR (left) and MR (right) image of a mouse brain with focal cerebral ischemia induced after MCAO. The EPR image shows two distinct regions corresponding to ischemia (thick arrow) and healthy tissue (thin arrow) due to lack of perfusion resulting from vascular occlusion preventing paramagnetic agent to reach the ischemic tissue. T2w MR image shows hyperintensity in the ischemic region due to tissue edema and accurately maps to the lesion shown on EPR image.