Imaging brain pH using hyperpolarized ^{13}C-labeled bicarbonate

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Introduction

It is well known that the blood-brain barrier blocks the uncontrolled movements of many solutes but allows rapid movement of selected substances such as glucose, oxygen and carbon dioxide; bicarbonate is also actively transported, albeit less rapidly [1]. Molecular imaging of the brain is limited by the requirement for the probe molecule to cross this barrier: a few small biomarkers may actively or passively cross the endothelial cells but when combined with an imaging label, transport will often be inhibited. Bicarbonate (HCO_3^-) forms the major cerebral buffer by conversion into carbon dioxide (CO_2) in the reaction catalyzed by the enzyme carbonic anhydrase [2]. We have previously shown that ^{13}C-labeled bicarbonate ($H^{13}CO_3^-$) can be polarized using Dynamic Nuclear Polarization (DNP) and that this can be used to image tumor pH *in vivo* [3]. We show here that hyperpolarized $H^{13}CO_3^-$ and $^{13}CO_2$ can be detected within normal mouse brain following the injection of hyperpolarized $H^{13}CO_3^-$. The spatial distribution of the two molecules can also be imaged and the calculated brain pH was shown to be lower than the surrounding tissues, in keeping with previous invasive microelectrode studies.

Methods

^{13}C-labeled cesium bicarbonate was hyperpolarized in a prototype polarizer (GE Healthcare). A surface coil was placed over the head of a mouse and 0.2 ml of ~100 mM hyperpolarized $H^{13}CO_3^-$ was injected into a tail vein. ^{13}C images were acquired from a 6 mm slice through the head of the animal using chemical shift imaging (CSI). False-color ^{13}C images were superimposed over the black and white ^1H MR images. pH was calculated from the relative concentrations of $H^{13}CO_3^-$ and $^{13}CO_2$ in each voxel using the Henderson-Hasselbalch equation and the pH of the brain was calculated from the voxels on CSI within the anatomical boundaries of the brain.

Results

The brain pH was calculated as 7.20 ± 0.08 (Average ± S.D.; n = 4). Imaging demonstrated that while $H^{13}CO_3^-$ was distributed throughout all of the tissues within the head of the animal, the $^{13}CO_2$ concentration was highest within the brain (Fig. 1B and 1C). The pH map (Fig. 1D) showed that the intracerebral pH was lower than the surrounding tissues.

Discussion

The results demonstrate that the spatial distribution of $^{13}CO_2$ and pH can be imaged using DNP in the brain; it is probable that the hyperpolarized $^{13}CO_2$ crosses the blood-brain barrier before interconverting with $H^{13}CO_3^-$ within the brain. The calculated brain pH is in keeping with published invasive microelectrode measurements of interstitial pH, which have been reported as 7.1-7.3 [2]. Potentially, this provides a new technique for imaging brain function as previous studies have shown that neuronal activation can be accompanied by changes in pH, although the measured pH changes have been small at ~0.1 pH units [2]. Many pathological conditions are associated with alterations in central nervous system pH such as ischemia [4], demyelination [5], and cancer [6]. This method therefore offers the possibility of a new cerebral imaging technique which could be applied to brain function and pathology: imaging brain pH and CO_2 are likely to provide novel biomarkers of cerebral disease and response to treatment.

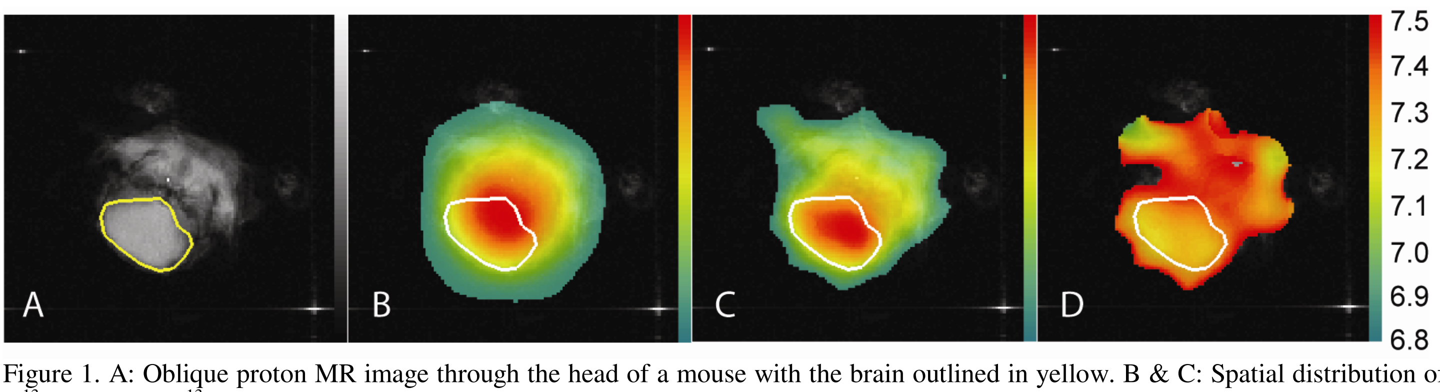

Figure 1. A: Oblique proton MR image through the head of a mouse with the brain outlined in yellow. B & C: Spatial distribution of $H^{13}CO_3^-$ (B) and $^{13}CO_2$ (C) in the same slice acquired using chemical shift imaging. D: pH map calculated from B and C with the brain outlined in white. The pH color scale is shown to the right of the image.

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References

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