Functional Brain Imaging of Pain Response Using Hyperpolarized Xenon MRI

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Purpose

Hyperpolarized xenon (HP ^{129}Xe) MRI is a new and innovative imaging method that relies on the detection of xenon (^{129}Xe) gas that is inhaled by the subject. Several characteristics make HP ^{129}Xe especially promising for studies of brain function and pathology. Namely, HP ^{129}Xe is highly lipid soluble and permeates biological membranes and myelin; HP ^{129}Xe is not inherent in biological tissue and so produces virtually no background signal; Xenon is considered an ideal perfusion tracer; and HP ^{129}Xe exhibits a large NMR chemical shift in different biological environments. Thus, unlike conventional proton imaging, HP ^{129}Xe may offer a means to measure brain function based on the chemical/oxygen environment in addition to measures based on blood flow. Our group previously demonstrated the use of HP ^{129}Xe to track blood flow changes evoked by vasodilation. The purpose of the present study was to evaluate the specificity to which HP ^{129}Xe MRI can map changes in brain activity by using it to image a well defined functional response evoked by a pain stimulus in the forepaw of a rat.

Method

All procedures were approved by the Institutional Animal Care and Use Committee. Imaging was performed on a 4.7 T/ 33 cm bore Bruker Biospec Advance system magnet controlled by a console running ParaVision software. A proton surface coil was used in combination with a ^{129}Xe surface coil to transmit and receive signals at both the proton (200 MHz) and xenon (55.35 MHz) frequencies. Five male Sprague-Dawley rats weighing between 200-250 g were initially anesthetized by a 1.5 ml/kg i.p. injection of a ketamine:xylazine mixture (57:8.5 mg/ml), and a tracheotomy was performed whereby the airway was catheterized with a 14-gauge, 3.5 cm catheter. The animal was placed on a modified ventilator and ventilated with 97% O_2 and 1.5% isoflorane so that anesthesia was maintained throughout the imaging procedure. Oxygen saturation and body temperature were measured throughout the experiment. The breathing rate was 40 breaths per minute with a 400 ms inspiration period, a 250 ms breath-hold period, and a 850 ms expiration period and an inter-breath interval of 1500 ms. A tidal volume of 2.5 to 3 ml was supplied for each breath. After the acquisition of a coronal proton slice image, the animal's left forepaw was injected with a vehicle solution and a ^{129}Xe chemical shift image (CSI) was acquired in the coronal plane (slice thickness 2.5 or 5 mm) while HP ^{129}Xe was administered using alternate breaths of ^{129}Xe and the O_2/isoflorane mixture, over a four minute period. Next, the chemical irritant capsaisin (20 ul of 3mg/ml) was injected into the animal's right forepaw, and a second CSI was acquired. Images acquired before and after administration of capsaisin were digitally subtracted to produce difference images that reflect changes in ^{129}Xe distribution evoked by the pain stimulus.

Results

HP ^{129}Xe MRI was able to map changes evoked by a pain stimulus with high anatomical specificity in the rat brain (N=5). Whereas baseline HP ^{129}Xe images showed some distribution in sub-cortical brain regions, images acquired following administration of capsaisin showed a significant increase of the HP ^{129}Xe signal in the cortical regions known to be responsible for the processing of pain information, namely the anterior cingulate, frontal, and somatosensory cortices (Figure 1). While activity in the anterior cingulate and frontal cortex was bilateral, unilateral activation of the somatosensory cortex was in the hemisphere contralateral to the forepaw injected, consistent with the activation pattern seen using conventional proton fMRI.

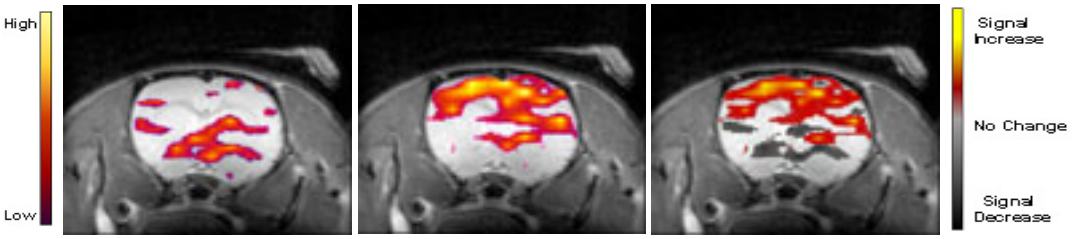

Figure 1. (a) Proton image of 1 mm coronal slice through the rat brain acquired with RARE sequence, TE=30 ms, TR=2000 ms, av=8, with falsecolor overlay of HP ^{129}Xe CSI image acquired after vehicle injection to the rat's left forepaw. The 2D CSI sequence consisted of 16 and 32 phase encoding steps in two dimensions, a phase gradient duration of 500 us, a flip angle of 11°, a TR of 500 ms, a FOV of 2.5 cm, and a slice thickness of 5 mm. K-space data was zero-filled to yield a linear reconstructed image of 32 x 64 pixels. **(b)** HP ^{129}Xe CSI image acquired after injection of capsaisin 3mg /ml to the right forepaw. **(c)** Difference image obtained by subtracting pre from post drug image shows localization of signal increase and decrease.

Conclusion

These results demonstrate that HP ^{129}Xe MRI can be used for functional brain imaging and that its anatomical specificity is comparable to conventional fMRI methods. Future directions include direct comparisons to conventional fMRI using BOLD and ASL, implementation of fast imaging sequences for acquisition of HP ^{129}Xe fMRI images, and development of HP ^{129}Xe functional imaging based on oxygen sensitivity. These endeavors will help to determine the ways in which the unique properties of HP ^{129}Xe can be utilized for functional and anatomical studies of the brain.

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