Visualization of Cortical Spreading Depression Using Manganese-Enhanced MRI

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Synopsis

Cortical spreading depression (CSD) was visualized for the first time using manganese-enhanced MRI (MEMRI) following topical application of 4M KCl to the exposed rat cortex. The region of MEMRI signal enhancement was confined to a 1.0-1.5-mm-thick cortical layer extending radially from the induction site. MEMRI allowed visualization of CSD over the entire cortical layer in the affected hemisphere. These results are consistent with previous studies of CSD using DWI and should be useful for investigating CSD itself as well as its role in cerebral ischemia.

Introduction

Cortical spreading depression (CSD) is characterized by a spontaneous and reversible depression of electrical activity that spreads from the site of onset as a radial wave across the cortex with a speed of 2-5 mm/min.[1] CSD is accompanied by an ionic redistribution across the cell membrane, with efflux of K^+ and influx of Na^+, Cl^-, $Ca^{2+}$and water. Recent studies have reported the use of Mn^{2+} as a membrane-depolarization-dependent contrast agent for monitoring neuronal activation following the application of glutamate,[2] as well as in the study of focal ischemia.[3] Extracellular accumulation of K^+ and/or glutamate is believed to play a central role in the propagation of CSDs. Since Mn^{2+} has an ionic radius similar to that of Ca^{2+}, and is transported into the cell in a manner similar to Ca^{2+}, it should be possible to use $Mn^{2+}$to track the spatial distribution of CSD using MEMRI.

Methods

Seven male Sprague-Dawley rats weighing 300-350g were anesthetized with an intraperitoneal injection of chloral hydrate (400 mg/kg). Manganese chloride ($MnCl_2$; Sigma), dissolved to 74.5mM in isotonic saline, was infused through the left femoral vein at a rate of 3.97µmol/min (3.2ml/hr) using a syringe pump (model 11; Harvard Apparatus) for 32 min. Ten minutes after start the of $MnCl_2$ infusion, 25% D-mannitol solution (5ml/kg; Sigma) was injected through the external carotid artery (ECA) over 2 min. For glutamate administration (N = 2), L-glutamic acid solution (0.2ml of 10mg/ml; Sigma) was injected through the ECA 22 min. after start of $MnCl_2$ infusion. For CSD (N = 2), the fronto-parietal cranium was exposed by a midsagittal incision, and a burr hole, 1.5 mm in diameter, was made in the right parietooccipital cortex 1 mm anterior and 1.5 mm lateral of the lambda. The dura was excised with a 23-gauge needle to expose the surface of the cortex. Application of 4M KCl was performed in the following manner, 22 min. after start of $MnCl_2$ infusion: 3 min. 4M KCl exposure, saline wash $\rightarrow$ 3 min. waiting period $\rightarrow$ 3 min. 4M KCl exposure, saline wash. For the corresponding controls (N = 3), physiologically buffered saline (NaCl) was applied in place of the glutamate or KCl.

MRI experiments were performed with a Bruker Biospin 2.0T/45 cm imaging spectrometer operating at 85.56 MHz for ^1H and equipped with ±20G/cm self-shielded gradients. T_1-weighted imaging was performed using the following acquisition parameters: TR/TE = 300.0/12.0 msec, FOV = 4 cm × 4 cm, matrix size = 256 × 256. For the glutamate administration group and controls, six 3-mm slices were acquired with NEX = 2. For the CSD group and controls, eight 2-mm slices were acquired with NEX = 4.

Results

Fig.1A shows the signal enhancement from T_1-weighted MEMRI following glutamate administration. Average enhancement in the cortex is 129% ± 5%. Fig.1C shows the signal enhancement from T_1-weighted MEMRI following CSD. Average enhancement in the cortex is 180% ± 20%. No significant changes in cortical signal intensity were detected for the saline control (Fig.1B) or the NaCl control for CSD (Fig.1D).

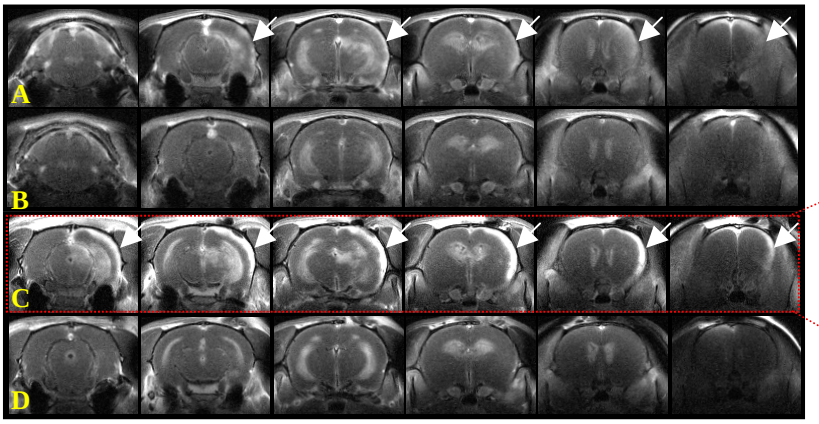

Figure 1: T_1-weighted MEMRI following glutamate administration and CSD. **(A)** Neuronal activation following glutamate administration. **(B)** Saline control. **(C)** Cortical enhancement following 4M KCl application. **(D)** NaCl application. Signal enhancement following CSD in the presence of Mn^{2+} is clearly visible in the right cortex of **(C)**. Arrows highlight regions of MEMRI enhancement.

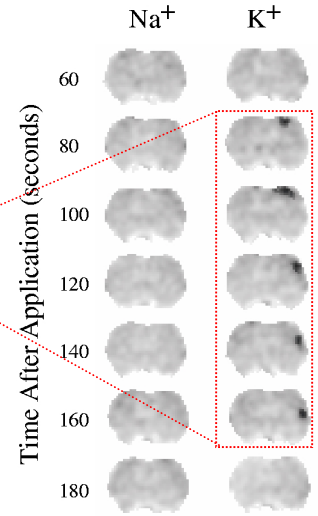

Figure 2: ADC maps for rat brain exposed to physiologically buffered saline (NaCl) and 3M KCl. The intensity is proportional to D_{app} and a nonlinear mapping, such that values of D_{app} below 0.55×10^{-5} cm^2 s^{-1} appear nearly black, allowing exaggeration of the affected region. The maps acquired after NaCl application appear the same and are indicative of a normal rat brain. After application of 3M KCl, a region of decreased diffusion coefficient, approximately 2 mm in size, is clearly visible moving away from the application site to the lower cortex. Reprinted from Ref. 4 with permission from Wiley-Liss, Inc.

Discussion

For CSD, the region of signal enhancement was confined to a 1.0-1.5-mm-thick cortical layer extending radially from the induction site. These results are consistent with previous studies of CSD using DWI (Fig.2), in which a region of decreased ADC, approximately 2mm in size, propagates away from the application site to the lower cortex. In contrast to the transient ADC changes accompanying DWI visualization of CSD, MEMRI "records" all cortical regions that have undergone CSD-induced depolarizations and thus CSDs appear as a hyperintense 'streak' down the cortex (Fig.1C). Given the relatively rapid propagation of CSDs relative to DWI acquisition, only a single slice visualization of CSDs is possible using this approach. In contrast, MEMRI has the advantage of multi-slice, whole-brain recording since the spatial history of CSD propagation is permanently recorded by the uptake of Mn^{2+}. This method should be useful for investigating CSD itself as well as its role in cerebral ischemia[3].

References

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