

Detection of Brain Activity during Chronic Pain Using Activity-Induced Manganese-Enhanced MRI in the Rat

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【Introduction】

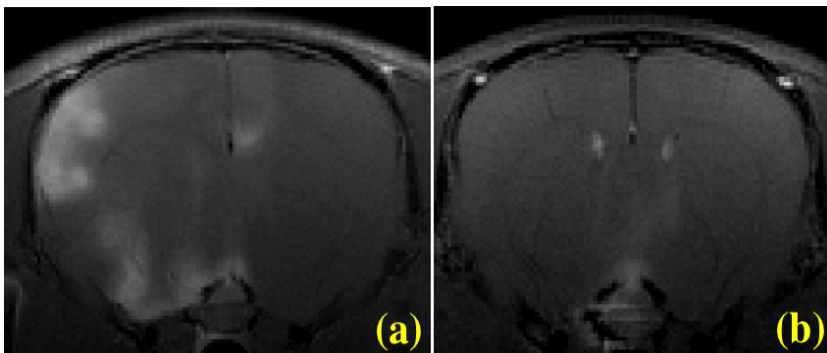
Nerve injury occasionally induces neuropathic pain, which is a type of chronic pain. The cardinal symptom of neuropathic pain is spontaneous or touch-evoked pain. Spontaneous pain is either continuous or paroxysmal. Touch-evoked pain consists of allodynia and hyperalgesia. Allodynia is pain triggered by innocuous stimuli, and hyperalgesia is an exaggerated response to painful stimuli. Non-invasive imaging techniques such as magnetic resonance imaging (MRI) are useful for the visualization of brain responses to pain. It has been reported that activity-induced manganese-enhanced (AIM) MRI is not influenced by hemodynamic changes and can be used for brain functional observation. Manganese is good contrast agent for MRI. In AIM MRI, manganese enters neurons through voltage-gated Ca^{2+} channels during a nerve activation and leads to signal enhancement in active brain areas. The purpose of this study is to detect brain activation during foot stimulation using AIM MRI in a segmental spinal nerve ligation (SNL) model. The SNL model is an experimental model of chronic pain that accompanies the tactile allodynia.

【Materials and Methods】

Male Sprague-Dawley (SD) rats ($n = 15$) were divided into two groups: SNL group ($n = 9$) and sham group ($n = 6$). The right L5–L6 spinal nerves were isolated and ligated distal to the dorsal root ganglia and proximal to the sciatic nerve formation with 5–0 silk sutures. Sham-operated rats underwent a similar surgical procedure, except that spinal nerves were not ligated. Animals were examined using AIM MRI at one or two weeks after the surgery. Rats were anesthetized with 2.5 % isoflurane for surgery. Polyethylene catheter (PE-50) were placed in the femoral artery and the vein to monitor blood pressure, sample blood gases and administer drugs. The right external carotid artery was also cannulated for drug administration. The blood brain barrier was disrupted by rapidly injecting 25% D-mannitol through the carotid artery. The sole of the right foot was stimulated with 5 Hz using brush while infusing the 25 mM MnCl_2 solution. After the stimulation, T_1 -weighted images were acquired using a 4.7-T MRI system (Bruker) with the following parameters: spin-echo, repetition time (TR)/echo time (TE) = 400/10.5 ms, field of view (FOV) = 32 mm, and matrix size = 256×256 , slice thickness = 1.0 mm, number of slices = 6, acquisition time for one set = 10 minutes. Image processing was performed using MRVision (MRVisoin Co., MA).

【Results and Discussion】

Pain-induced brain activation was successfully visualized using AIM MRI. Significant signal enhancement was observed in the second somatic sensory (S2), caudate putamen (CPu), and ventral pallidum (VP) areas. The area extending from the S2 cortex to the brainstem and thalamus is known as the pathway of somatosensory discriminative pain. In addition, the amygdala and medial regions of the frontal lobe are associated with the affective component of pain. Therefore, these results suggest that the AIM MRI is useful for the depiction of the conducting pathway of pain. Furthermore, it may be useful for investigation of the neural connections that receive and modulate pain signals. Diagnostic imaging of chronic pain will play an important role in the clinical treatment of pain and the development of pain-relieving drugs.



The typical images of the activity-induced manganese-enhanced (AIM) MRI

- (a) Segmental spinal nerve ligation (SNL) model
- (b) Sham-operated model

In AIM MRI at the brush stimulation of the right hind leg sole for SNL model, a high signal intensity change was observed in the second somatic sensory (S2), caudate putamen (CPu), and ventral pallidum (VP) areas. On the other hand, the signal enhancement was not observed in the sham-operated model.