Negative Functional MRI Changes in Capsaicin-Induced Painful Stimulation in Rats

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Introduction

An increasing number of studies, utilizing functional magnetic resonance imaging (FMRI), of pain processing in the human brain have identified areas of activation and "deactivation." It is well accepted that increases in the Blood Oxygenation Level Dependent (BOLD) signal intensity indirectly reflect neuronal excitation. However, the origin of the inverse phenomenon, a paradigmatic decrease in BOLD signal, remains speculative. FMRI studies on humans have identified significant decreases in BOLD signal intensity in medial parietal, posterior and perigenual cingulate cortex and medial prefrontal cortex during somatosensory pain (1,2). Similar observations were made with Positron Emission Tomography; regional cerebral blood flow decreases were detected in somatosensory cortex during anticipated painful stimulation (3) and during noxious stimulation in cingulo-frontal transition cortex and posterior cingulate gyrus (4).

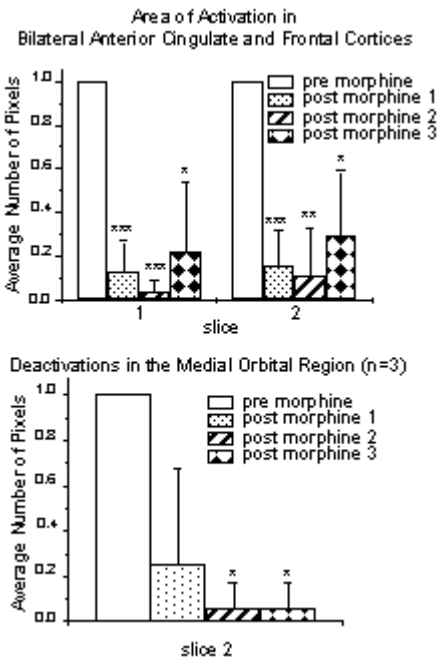
Animal studies involving nociceptive stimulation show activations of the anterior cingulate and somatosensory cortices (5) consistent with those made in humans (1). To date, paradigmatic decreases in BOLD signal have not been reported in an animal model of pain. Here we report observation of the paradigmatic BOLD signal decreases in a rat model of capsaicin-induced painful stimulation and morphine analgesia. Capsaicin is the active ingredient of hot peppers and produces an intense pain reaction following activation of specific receptors referred to as the vanilloid receptor. Thus, administration of capsaicin produces a "clean" pain response in a pharmacologically relevant manner.

Methods

Experiments were performed using a 9.4T/21cm horizontal bore magnet (Magnex, U.K) with an Avance (Bruker, Germany) console and a surface coil tuned to 400.5 MHz centered over the forebrain. The rats (n=6) were anesthetized with α-chloralose, ventilated and placed in the bore of the magnet. Sequential T2* images were acquired using a multi-slice gradient echo fast imaging sequence (TE = 25 ms, TR = 70 ms, 128 x 128). A total of 40 T2* images were collected in each imaging sequence. The experimental protocol involved an initial stimulation with capsaicin (25 µl of 128 µg/ml solution injected subcutaneously into the forepaw). Morphine was then administered by intravenous injection at a dose of 3 mg/kg. The capsaicin stimulation experiments were repeated three more times per animal following the administration of morphine. Thirty minute intervals were allowed between capsaicin injections. The sets of gradient echo images were analyzed using software based on fuzzy cluster analysis (EvIdent™).

Results

Following capsaicin injection, we observed a regional increase in the BOLD signal intensity in the MR images in all animals. Anterior cingulate (bilateral), frontal and sensory-motor cortices showed activation upon injection of capsaicin. Regional signal decreases which were the inverse of the activation time course were observed in 5 of the 6 animals. Of these 5 animals, 3 showed paradigmatic decreases in the medial orbital region of the brain (slice 2). The remaining two animals showed deactivations in the anterior frontal cortex region and only 2 pixels (pre-morphine) representing deactivation in the medial orbital region and therefore, were not included in the analysis. Following morphine administration (Figure), there were significant decreases in the areas of activation and corresponding decreases in the areas of deactivation.



Number of pixels corresponding to activation (top) and deactivation (bottom) following capsaicin injection (normalized to pre-morphine). Asterisks represent p*<0.005, p<0.001 and p***<0.0001 between pre- and post-morphine, capsaicin experiments.**

Discussion

Brain regions can be repeatedly activated with capsaicin injection provided the receptors are allowed 30 minutes to recover. Deactivations corresponding to the time course can be clearly observed in the medial orbital region of the rat brain. These deactivations in the rat correspond with regions of the brain known to show paradigmatic signal decreases in humans during noxious stimulation. The physiological mechanisms underlying the origin of paradigmatic BOLD signal decreases are not known. It has been suggested that deactivations could be the result of a normalization procedure artifact, a decrease in firing rate significant enough to affect blood flow or glucose utilization (6), passive hemodynamic shunting and disinhibition (7).

The decrease in the amount of deactivation and corresponding decrease in activation observed upon treatment with morphine suggests the decreases are a neurological effect. Whether the paradigmatic fMRI signal decreases are directly related to the BOLD effect remains to be determined.

References

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