The effect of morphine on footshock-induced brain activity: A preliminary fMRI study

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Abstract

In previous studies, we have found that electrical stimulation on the hind paw of rats successfully elicit BOLD fMRI activation in several regions of the cerebral cortex. This preliminary study explored the effect of morphine on such kind of footshock-induced brain activity. Rats were anesthetized by alpha-chloralose (20 mg/kg/hr, i.v.) and received electrical stimulations on the left hind paw during three sessions of fMRI scanning. The footshock-induced BOLD fMRI was recorded in the first "Baseline" session. The effect of morphine (10 mg/kg, i.v.) was evaluated in the second "Drug" session. Three hours later, the BOLD siganals were measured in the third "Recovery" session. In replication of our previous result, footshock-induced BOLD activation was found in both primary somatosensory cortex (SI) and anterior cingulate cortex (ACC) in the "Baseline" session. In addition, the BOLD activations of both regions were significantly decreased after morphine administration in the second session, and recovered in the third session. These results indicate that morphine could inhibit brain activities in these cortices, which may be related to its analgesic effect.

Introduction

Functional magnetic resonance imaging (fMRI) is a powerful tool in detecting the functional responses in the brains. Brain activations are indicated indirectly by blood oxygenation level-dependant (BOLD) contrast [1]. Imaging studies in humans and animals have demonstrated local activation of a number of different brain centers in response to painful stimuli. In previous studies [2], we have found that electrical stimulation on the hind paw of rats successfully elicit BOLD fMRI activation in several regions of the cerebral cortex. Such stimulation frequency-dependent BOLD activations were significantly stronger under alpha-chloralose than under pentobarbital anesthesia. In another report, it has been suggested that functional imaging in alpha-chloralose anesthetized animals provides an ideal model for the testing of novel analgesics [3]. The major aim of the present study is using fMRI to explore the effect of morphine on footshock-induced brain activity.

Material and Methods

Long-Evans rats (n = 8) weighting 220-350g were used in this study. Each rat was initially anesthetized by halothane (4%), and the femoral vein was cannulated for intravenous drug administration. Then the trachea was exposed and a cannula was inserted for monitoring ET-CO_2 and future suctioning of the airways. The rectal temperature was maintained at 36.5°C by a circulation water pad surrounding the animal in the scan chamber. The rat fMRI experiments were performed in an active shielded 900mm bore size 3T Bruker MRI/MRS system (Bruker BIOSPEC Gradient system S116, Bruker, Karlshruhe, Germany). The magnet was equipped with a 120mm inner diameter self–shielded gradient system (max. gradient strength 200mT/m; min. inductive rise time 250μs) and Radio frequency pulses were transmitted by a self-developed surface coil with diameter of 4 cm. Anatomical image were obtained using a Bruker implementation of Turbo-RARE sequence (TR = 1869.5ms, TE of 14.5ms, matrix size= 256×256, FOV = 60×60mm, NEX=4). Employing a BLIP Echo Planer Imaging, fMRI imaging was performed in the rat brain on 8 axial slices of 2 mm thickness without gaps (effective TE=30ms, matrix size=128×128, FOV = 60×60mm, NEX=2). The total scanning time of each image is 5 sec. In a box-car block design, electrical stimulations (3 Hz, 2mA, 2 ms) were applied to the left hind paw during scanning of 10 images and then stopped for the next 10 images. Each session consisted of 120 scan images. A total of three scan sessions were performed for each rat. The footshock-induced BOLD fMRI was recorded in the first "Baseline" session. The effect of morphine (10 mg/kg, i.v.) was evaluated in the second "Drug" session. Three hours later, the BOLD fMRI were measured in the third "Recovery" session. The result were analyzing by the FACT software (Functional MRI Analysis and Clustering Tools, written by K.H. Chuang, *et al.*). All Surgical and recording procedures were approved by the Animal Use and Care Committee of the National Taiwan University.

Results and Discussions

The fMRI results shown in Figure 1 indicated that footshock-induced BOLD activation was found in both primary somatosensory cortex (SI) and anterior cingulate cortex (ACC) in the "Baseline" session. After morphine administration, the BOLD activations of both regions were significantly decreased. Three hours later, the BOLD activations were recovered in the third session. For the BOLD signal changes in both regions (Figure 2), these data were analyzed by a one-way repeated measure ANOVA with "Session" as a within-subject variable. The analysis showed that the Session main effect was significant in both SI and ACC regions ($F(2, 14) = 8.16$, $p < .01$; $F(2, 14) = 7.73$, $p < .001$, respectively). Furthermore, post-hoc Scheffe tests showed that the BOLD activations of these areas during "morphine" session were significantly lower than other two sessions. These results indicate that morphine could inhibit pain-related brain activities in these cortices, and this inhibition may be related to its analgesic effect.

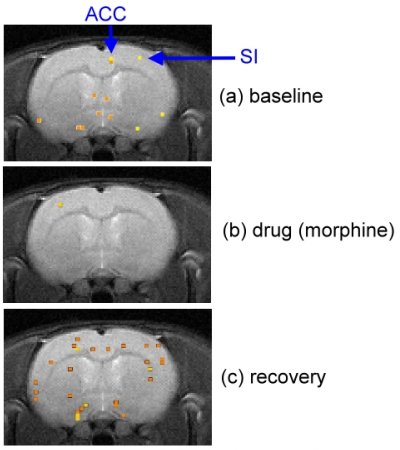

Figure1. The effect of morphine on footshock -induced brain activities.

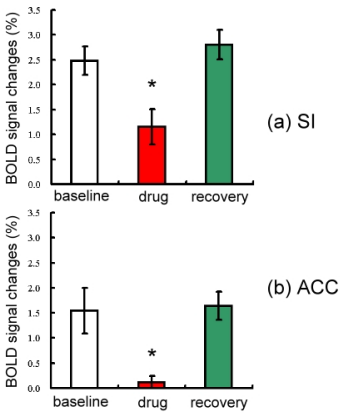

Figure2. The BOLD signal of the SI and ACC across three sessions.

References

[1] Ogawa, S., T. M. Lee, A. Nayak and P. Glynn. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn. Reson. Med., 14(1)*:68-78, 1990.

[2] Kuo, C.-C., Huang, I.-S., Tsai, G.-Y., Chen, J.-H., and Yen C.-T. Correlation of fMRI and ensemble neuronal activations in primary somatosensory cortex of the rat. Submitted.

[3] Tuor, U.I., Malisza, K.L., et al. Functional magnetic resonance imaging in rats subjected to intense electrical and noxious chemical stimulation of the forepaw. *Pain, 87*:315–324, 2000.