CBV-weighted fMRI study of Neurovascular Coupling in the Caudate Putamen following Graded Electrical Stimulation in the Forepaw of Rats

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Synopsis

This is the first imaging study that demonstrates the role of caudate putamen in pain-induced neurovascular processing. By evaluating CBV responses following graded electrical stimulation (5 – 60V), salient bilateral vasoconstriction effect was observed specifically in the caudate putamen, while vasodilation only appeared in the contralateral somatosensory cortex.

Introduction

Accumulative evidence suggests that caudate putamen (CPu) plays an important role in complex sensory-motor processing as well as nociception [1]. However, the involvement of CPu in nociception was difficult to be observed in BOLD fMRI studies [2,3]. One possibility causing minimal BOLD signals in this region may be vascular inhibition of the local BOLD response such as vasoconstriction effects since the modulation of major neurotransmitters in CPu (i.e. dopamine) is known to induce vasoconstriction [4]. To identify whether CBV of CPu is altered in pain processing, CBV-weighted fMRI technique was employed. Graded electrical stimulation was used to induce innocuous and nociceptive responses. The findings are important in revealing the missing role of the CPu in neurohemodynamics modulation under nociceptive stimuli.

Material and Methods

Five adult male Wistar rats of 250-300 g body weight were initially anesthetized by 3% isoflurane. A PE-50 catheter was inserted into the left femoral vein for anesthetic and contrast agent administration. After the rats were positioned on a stereotaxic holder, α-chloralose (70 mg/kg) was used for subsequent anesthesia and body temperature was maintained using a warm-water circulating system. Images were acquired only when the rat was in a stable condition where the ventilation rate was 55-60/min and the end-tidal CO_2 concentration was 3-3.5%. The femoral artery was cannulated for sampling the arterial blood parameters where significant changes in $PaCO_2$ and PaO_2 were not observed. All images were captured using a 4.7 T Biospec 47/40 spectrometer. Three slices, sixty repetitive gradient echo images were acquired (bregma +0.7 mm, -0.8 mm, and -2.3 mm) with a TR of 150 ms, TE of 20 ms, FOV of 2.56 cm, SLTH of 1.5 mm, NEX of 1, an acquisition matrix of 128×64 (zero-filled to 128×128). The CBV-weighted fMRI was performed by intravenously injection of 30 mg Fe/kg USPIO (Industrial Technology Research Institute of Taiwan, ROC) [5]. The relaxivities R_1 and R_2 of the USPIO are 53.6 $mMsec^{-1}$ and 359.8 $mMsec^{-1}$, respectively. For the electrical stimulation, two needle electrodes were inserted under the skin of the right forepaw and then fixed with surgical tape. Graded stimulation of 5V, 10V, 20V, 40V, and 60 V with 0.5 ms duration at 3 Hz were used and simple off-on-off paradigm was selected for detecting the responses of electrical stimuli, while the first and last 20 frames were categorized as baseline, and the middle 20 were collected during stimulation. All images were analyzed using Matlab and custom-built ISPMER system [6].

Results and Discussion

Fig. 1 clearly shows the vasodilation effect in contralateral primary somatosensory cortex of the forelimb region (S1FL) following 60V electrical stimuli. The vasodilation in this area can directly correlate with the local neuronal activation; however, specific and bilateral vasoconstriction effect was observed in the CPu. This phenomenon can be also shown in Fig. 2 that illustrate the incidence response of 5 rats with graded electrical stimulation (5-60V). Under different stimulation intensities, the S1FL always preserve similar spatiotemporal orientation, but the CBV in CPu was gradually constricted with the increase of stimulation intensity. Vasoconstriction occurring in the CPu is intriguing yet still elusive. We suspected that this effect may be mediated by dopaminergic transmission since dopamine D_2 receptor was proposed to involve in pain modulation [7,8] and would also significantly alter the neurovascular coupling in CPu. Previous study reported that injection of D_1/D_5 receptor agonists would induce positive increases in CBV, but the D_2/D_3 agonists, in contrast, resulted in negative changes of CBV [4]. Thus, we hypothesized this specific vasoconstriction effect may be mediated by the functions of dopamine D_2 receptors.

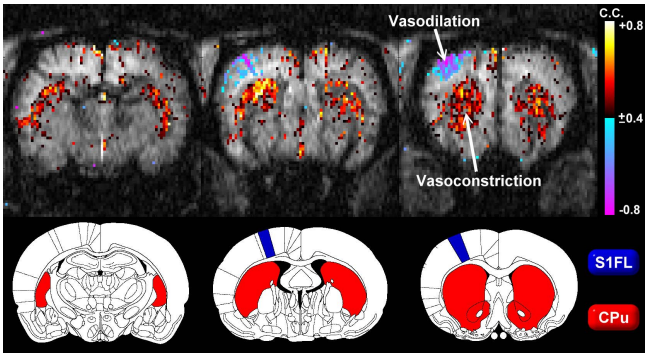

Fig. 1 CBV-weighted MR images were generated through correlation coefficient method, where positive and negative MR signal changes were coded by hot and cold colors, respectively.

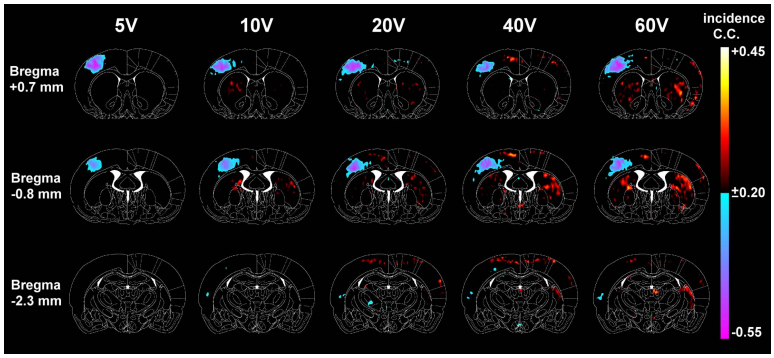

Fig. 2 Incidence images were calculated by averaging the correlation coefficient maps for the 5 rats. Each correlation map was registered to the rat brain atlas before averaging.

Conclusion

The present study demonstrates the CBV responses following graded electrical stimulation. The specific vasoconstriction effect was observed in CPu with the increase of stimulation intensity. This intriguing finding may indicate the involvement of dopamine D_2 receptor in the nociception.

Reference

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