Endogenous opioid-dopamine neurotransmission evokes sustained negative CBV-weighted fMRI responses

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Introduction

Dopamine is the major neurotransmitter that plays a critical role in normal brain functions. Abnormal dopamine levels have been associated with many neurological disorders, such as Parkinson's disease and drug addiction [1]. We recently showed evidence that peripheral noxious stimulation elicits negative CBV-weighted fMRI signals in the striatum despite an increase in neuronal activity [2] and that intravenous injection of a dopamine D_2/D_3 receptor antagonist reduced the magnitude of the stimulation-induced CBV-weighted fMRI responses. There is also evidence that the hemodynamic fMRI signal is highly dependent on the types of receptor subtypes being activated [3]. Because dopamine-induced vasoconstriction evoked by noxious stimulation and μ-opioid receptors is known to mediate nociception [4] as well as the activity of dopaminergic neurons [5], it is important to clarify the contribution of various opposing factors on the hemodynamic fMRI responses for proper interpretation of the fMRI data. In this study, we employed CBV-weighted fMRI with noxious electrical forepaw stimulation to investigate the sources of the negative fMRI signals using μ-opioid receptor and dopamine D_2/D_3 receptor modulations.

Material and Methods

CBV-weighted fMRI with intravenously administered iron oxide contrast agent (30 mg Fe/kg, Resovist) was performed on 10 adult male Wistar under alpha-chloralose (70 mg/kg, i.v.) anesthesia. Animals were subjected to unilateral 10-mA electrical stimulation (3-Hz square wave, 0.5-ms pulse duration) of the forepaw to induce vasoconstriction in the striatum, as described previously [2]. Morphine (5 mg/kg, i.v.) was then used to activate μ-opioid receptors, whereas naloxone (0.7 mg/kg, i.v.) was used to antagonize the μ-opioid receptors. In addition, eticlopride (1 mg/kg, i.v.) was used to study the opioid-dopamine D_2/D_3 receptor interaction. MR images were captured using a 4.7-T Bruker Biospec 47/40 spectrometer A FLASH sequence comprising 60 time frames was used for CBV fMRI experiments with a repetition time of 150 ms, echo time of 20 ms, flip angle of 22.5°, field of view of 2.56×2.56 cm, slice thickness of 1.5 mm, number of excitation of 1, acquisition matrix of 128×64 (zero-filled to 128×128), and temporal resolution of 9.6 s. An OFF–ON–OF paradigm was used to detect the responses to electrical stimulation. All images were analyzed using Matlab and custom-built image processing software [6,7].

Results and Discussion

Unilateral stimulation of the forepaw elicited vasodilation in the contralateral primary somatosensory cortex (cS1) and concurrent salient bilateral vasoconstriction in the striatum. Preinjecting saline as a vehicle control induced no changes in the CBV fMRI response. Pretreatment with morphine caused a profound reduction in CBV fMRI responses in both the cortical and striatal areas during noxious forepaw stimulation (**Fig.1**). The effect of morphine decreased gradually over time, until by 30 min after morphine injection the CBV-weighted images had reached a pattern similar to that of the control CBV fMRI response. The injection of naloxone not only reversed the residual morphine effect, but also predominantly eliminated the entire vasoconstrictive response in multiple brain regions and led to a stronger vasodilation in the cS1. This demonstrates unequivocally that endogenous opioids are involved in the generation of stimulation-induced negative fMRI signals. The morphine-enhanced vasoconstriction observed in both the cortical and the striatal areas occurs independently of general physiological autoregulation since noxious stimulation is known to increase the heart rate and arterial blood pressure, while both of these factors should increase the blood flow. Eticlopride was given to another group of rats following the first scan after morphine treatment. A clear blocking effect of eticlopride was also observed (**Fig.2**). This indicates that the nociception-induced negative fMRI signals in the brain are driven by opioid–dopamine interactions, and that without either of these neurotransmitters the negative signals cannot be present.

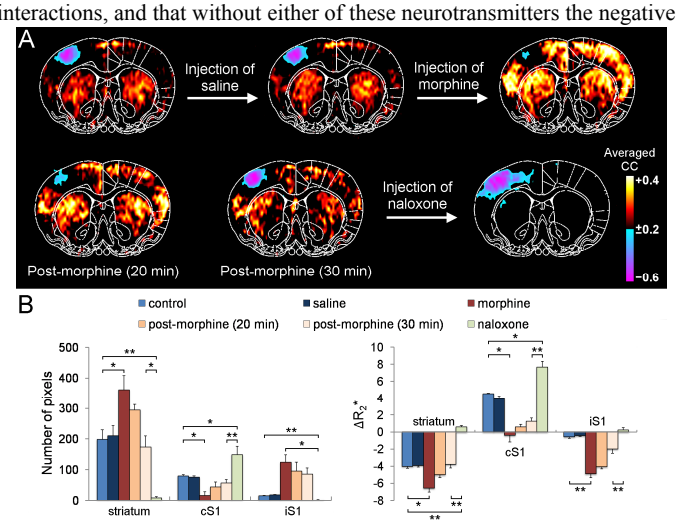

Fig. 1 Effects of morphine and naloxone on nociception-induced negative fMRI signals. (**a**) Averaged correlation coefficient (CC) maps of five rats acquired at bregma +0.7 mm. (**b**) The responsive area was quantified by the number of responsive pixels (P<0.05, paired t-tests compared with baseline) in the region, and the degree of CBV changes is quantified by ΔR_2* values (s^{-1}). *, ** Statistically significant levels at P<0.05 and P<0.01, respectively. Error bars are s.e.m. values.

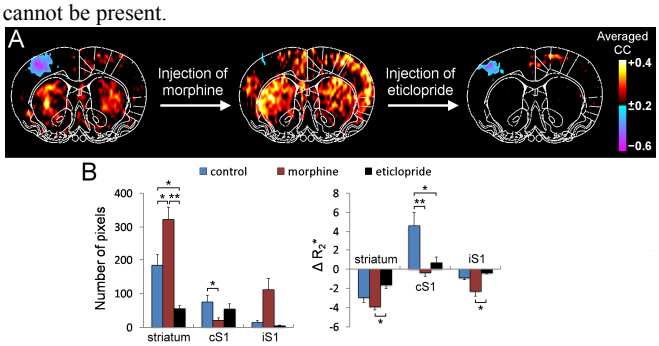

Fig. 2 Opioid-enhanced vasoconstriction is mediated by the activation of dopamine D_2/D_3 receptors. (**a**) Averaged correlation coefficient (CC) maps of five rats. (**b**) The responsive area and the degree of CBV changes

Conclusion

This study sheds light on the endogenous contribution of opioid and dopamine D_2/D_3 systems to a particular hemodynamic response. Sustained negative CBV fMRI responses are detected concomitantly with sequential activation of opioid and dopamine D_2/D_3 receptors. This vasoconstriction may counteract the positive CBV responses that are often detected associated with increased neuronal activities. The complex interplay of competing vasodilatory and vasoconstrictive effects of neurotransmission in the present of increased neural activity need to be taken into account for reliable interpretation of hemodynamic-based fMRI data.

References

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