Imaging dopamine autoreceptor activity using functional MRI as a novel technique in Parkinson¡¦s disease

Chiao-Chi V Chen[1], Yi-Hua Hsu[1], Chien-Yuan E Lin[2,3], and Chen Chang[1]

[1]*Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan,* [2]*GE Healthcare, Taipei, Taiwan,* [3]*MR Advanced Application and Research Center, GE Healthcare, China*

Purpose

Dopamine autoreceptors represent a very critical player that regulates dopaminergic function. They are classified as D2 autoreceptors and the only dopaminergic receptor type found in the soma, dendrites, and axonal terminals of dopaminergic neurons. Other dopaminergic receptors (D1-D5) are mainly expressed postsynaptically in non-dopaminergic neurons. Up to date, no dopamine autoreceptor imaging is made available, and thus limited is known regarding the role of D2 autoreceptors and aberrations in Parkinson's disease (PD).

Previous studies have shown that, when applying noxious electrical stimulation to a rat forepaw, reduced cerebral blood volume (CBV) is observed in the bilateral striatum[1]. This evoked CBV decrease is completely abolished by a D2 antagonist eticlopride. Despite not having been specifically linked with the dopaminergic autoreceptor function, the nociception-evoked CBV reduction is predominated by the presynaptic input, i.e. the nigrostriatal pathway[2]. The distribution of the CBV decrease well corresponds to that of the nigrostriata dopaminergic fibers, as demonstrated in Parkinson's disease rats[3]. Moreover, the response was significantly abolished when the substantia nigra was inhibited, but unaltered when the striatum was inhibited[2]. Based upon these preceding findings, this pain-evoked striatal response is very likely to reflect autoreceptor activity. In this study, we validated this concept and gained understanding about how this dopaminergic regulator (D2 autoreceptor) is affected in PD.

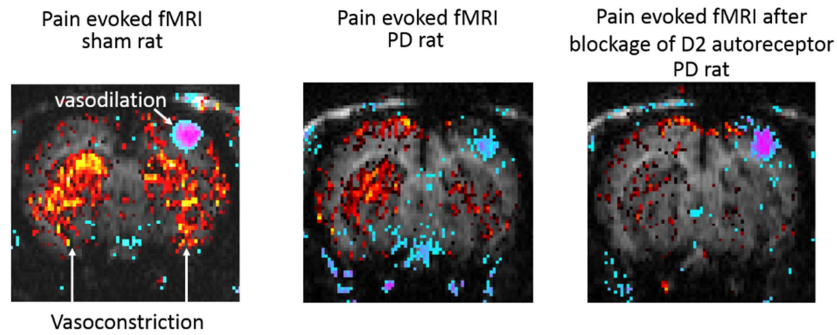
Methods

PD rat induction: Right SN was lesioned by infusing 6-OHDA at 15 ug/kg and validated by the rotational test with ipsilateral turns of more than 6 per minute.

CBV weighted fMRI: On D14 after PD induction, anesthesia was initiated with 3–5% isofluorane in O_2 flowing at 3–5 L/min. For the CBV-weighted fMRI study, superparamagnetic iron oxide coated with PEG (ITRI, Hsinchu, Taiwan) were administered as a contrast agent at a dose of 20 mg Fe/kg. The negative CBV response of the striatum to noxious stimuli was induced by the application of noxious, nociceptive electrical stimulation to the rat forepaw. Stimulation adhered to an off–on–off–on–off paradigm, which would be correlated pixel-by-pixel with the corresponding image signals to generate the CBV correlation maps. Images were acquired at 4.7T using a FLASH (Fast / Low Angle SHot) sequence with a repetition time of 150 ms, echo time of 15 ms, flip angle of 22.5°, field of view of 2.56 cm by 2.56 cm, slice thickness of 1.5 mm, 1 excitation, acquisition matrix of 128 by 64 (zero-filled to 128 by 128), and temporal resolution of 9.6 s. A series of 60 images were acquired during each stimulation paradigm.

Pharmacological testing: A D2 autoreceptor blocker AJ76 was given intravenously to a PD rat at the dose of 2.5mg/kg and its effects on CBV-fMRI were assessed.

Results



The left figure indicates a sham rat exhibiting strong vasoconstriction in the bilateral striatum. The vasodilation seen in the right cortex centered in the primary somatosensory cortex (S1). In a PD rat (the middle figure), the vasoconstriction response in the lesioned(right) striatum was diminished while the left striatal vasoconstriction and S1 vasodilation remained intact. After administering the D2 autoreceptor blocker AJ76 (the right figure), the vasoconstriction in the intact striatum and the remaining vasoconstriction in the lesioned striatum were diminished significantly. Interestingly, the S1 vasodilation remained large after the treatment.

Discussion and conclusion

Previously we only knew the striatal vasoconstriction was D2 mediated[1, 2]. In this study we further obtained evidence that the vasoconstriction in the striatum is likely a dopamine D2-autoreceptor specific response, and this activity well reflects the integrity of the dopaminergic system. This information supports the value of this pain evoked fMRI technique as a useful technique to assess PD.

References

1.Shih, Y.Y.I., *et al.* A New Scenario for Negative Functional Magnetic Resonance Imaging Signals: Endogenous Neurotransmission. *J Neurosci* 29, 3036-3044 (2009). 2.Hsu, Y.H., Chang, C. & Chen, C.C.V. Negative cerebral blood volume fMRI response coupled with Ca2+-dependent brain activity in a dopaminergic road map of nociception. *Neuroimage* 90, 43-51 (2014). 3.Chen, C.C.V., Shih, Y.Y.I. & Chang, C. Dopaminergic imaging of nonmotor manifestations in a rat model of Parkinson's disease by fMRI. *Neurobiol Dis* 49, 99-106 (2013).