L-Tetrahydropalmatine administration induces region-specific BOLD responses in the mesocortical limbic network of the human brain

L-P. Fu[1], G-H. Wu[2], Z-T. Zou[3], D-J. Li[3], Y-C. Shao[1], G-H. Bi[1], L. Ma[3], S-J. Li[2], and Z. Yang[1]

[1]Beijing Institute of Basic Medical Science, Beijing, Beijing, China, People's Republic of, [2]Department of Biophysics, Medical College of Wisconsin, Milwaukee, Wisconsin, United States, [3]General Hospital of People's Liberation Army of China

INTRODUCTION

L-tetrahedropalmatine (L-THP, or commercial name Rotundine), is a traditional Chinese herbal medicine, extracted from *Corydalis* [1]. As a central relaxant, the pharmacological effects of L-THP are analgesia and anxiety relief [1]. A profile of L-THP reveals that it binds to dopamine receptors [2]. Behavioral experiments using rats have demonstrated that L-THP could inhibit self-administration behaviors in cocaine-, heroin- and morphine-dependent rats. This active alkaloid has no addictive potential. Clinically, L-THP can attenuate the protracted withdrawal symptoms and decrease the level of self-reported craving in heroin-dependent human subjects [3]. However, the neurobiological responses and action sites of L-THP in the human brain have not been studied. In the present study, an fMRI method is employed to investigate human brain responses upon acute administration of L-THP.

MATERIALS AND METHODS

Subjects Twenty healthy young men (24.1±1.9 years old) participated in the study after written informed consent was obtained. Thirteen subjects received an intramuscular injection of L-THP with a dose of 1.5 mg/kg in 3-ml sulfate solution (Nanning Best & Wide Pharmaceutical Co., LTD, Guangxi, China). The other 7 subjects received 3-ml saline as a vehicle treatment in a randomized double-blind design. ***fMRI acquisition***: All subjects received three scans: an SPGR high-resolution anatomical scan, a 30-min fMRI-BOLD scan in which the 1.5 mg/kg of L-THP was injected 5 min into the scan, and a 25-min continuous fMRI-BOLD scan. All images were acquired at a 3.0 T GE Excite HD scanner using a standard GE head coil. The imaging parameters for SPGR acquisition are: TR of 22 ms, minimum full TE, thickness of 1.0 mm, matrix of 256×256, FOV of 24 cm. The whole-brain functional images were acquired using a turbo-segmented EPI sequence [4] with z-shimmed background compensation (effective TR of 6 s, TE of 25 ms, bandwidth of 125 kHz, matrix of 64×64, FOV of 24 cm, 5-mm slice thickness and 1-mm spacing, 24 axial slices). ***Data Analysis*** All the fMRI data were processed with AFNI software. Among the 13 participants, the data of 4 were eliminated due to excessive head motion (elimination criteria: translational motion > 2.5 mm and rotation > 2.5°) after motion detection and correction procedures. The fRMI data from two scans were concatenated into a single dataset and the BOLD responses from the L-THP injection were fitted with a nonlinear least-square algorithm to a Beta model. The area-under-the-curve (AUC%) was calculated from the fitted curve. The AUC% maps were transformed into a common Talairach space for comparison across subjects and spatially filtered (Gaussian filter with a full width at half maximum of 6 mm) to reduce the uncertainty of common space transformation. A one-sample *t*-test on the AUC% against 0 (no response) was performed. A cluster threshold at the $P < 0.05$ level was used, accounting for multiple comparisons (individual voxel threshold at $P < 0.05$, minimum cluster size = 2700 μL), which was determined by a Monte Carlo simulation of simultaneous statistical tests based on the brain mask.

RESULTS

The acute L-THP administration induced significant brain responses, as shown in Figure 1. The treatment using L-THP produced positive and negative BOLD signals. The most negative BOLD response was found in the regions of the basal ganglia area and the limbic system such as the lentiform nucleus, globus pallidus, thalamus, amygdale, mammillary body, hippocampus gyrus and substantia nigra, etc. The positive BOLD responses occurred in the regions of the cuneus, precuneus, cerebellum, and inferior temporal cortex.

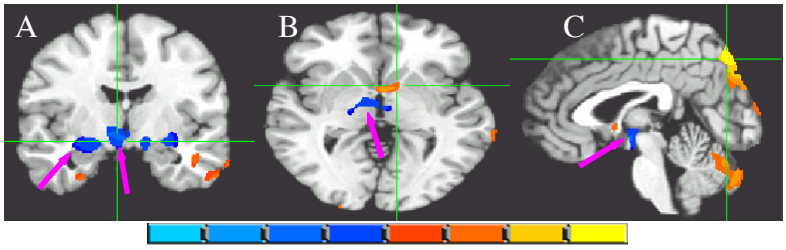

Figure 1. The coronal (A, Y = -8 mm), axial (B, Z = 0 mm) and sagittal (C, X = -3 mm) activation maps show the L-THP induced positive and negative BOLD signal in the mesocortical limbic systems that are related to reward, learning and memory circuits. The pink arrows point to the regions with negative BOLD responses (blue). The threshold for statistical significance is set with $P < 0.05$.

DISCUSSION AND CONCLUSION

L-THP significantly induced region-specific BOLD signals in the mesocortical limbic network. These network-specific responses indicate that the action sites of L-THP are related to the dopaminergic systems. Since L-THP significantly binds to the dopaminergic receptors of D1, D2, and D3 and is a known D2 antagonist, it is conceivable that these activated brain regions are related to the dopaminergic activity and its projected areas. Although the detailed mechanisms responsible for the positive and negative BOLD responses are not fully understood, L-THP could regulate activity of dopaminergic systems. Since drugs of abuse are related to the adaptation of the mesocortical limbic systems, it is suggested that L-THP could have great potential to reverse or attenuate adaptation in treating psychological and physical dependence for drug users.

REFERENCE

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