BRIEF RESEARCH COMMUNICATION

(−)-Linalool influence on the cerebral blood flow in healthy male volunteers revealed by three-dimensional pseudo-continuous arterial spin labeling

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ABSTRACT

Background: Although aromatherapy is widely used, the pharmacology of the essential oils remains undiscovered.
Aim: The present study assessed the effect of (−)-linalool, the main contained material of lavender, on the brain function.
Materials and Methods: Healthy male volunteers calculated the regional cerebral blood flow (CBF) before and after inhalation of (−)-linalool, and CBF changes were evaluated.
Results: There were significant CBF reductions in the right superior temporal gyrus to insula, anterior cingulate cortex after inhalation.
Conclusions: The previous study detected the regulatory influence of (−)-linalool on the glutamatergic transmission. The effect of (−)-linalool on the ACC and insula would cause the sedative and anxiolytic activity.

Key words: Aromatherapy, glutamatergic transmission, lavender, (−)-linalool, pseudo-continuous arterial spin labeling

INTRODUCTION

The odors of essential oils are used in the treatment of depression, anxiety, and some types of cognitive disorders in aromatherapy. The lavender, the essential oil that has been the most widely investigated, showed the sedative and anxiolytic activity.¹ Lavender contains the linalool as the main component. The previous study showed that linalool can be detected in mice at a high concentration in blood samples from the retrobulbar venous plexus after inhalation of it.² This point suggested that linalool was absorbed by inhalation and consequently might elicit the effects on the central nervous system. Psychopharmacological in vivo evaluation of linalool detected that this compound has marked dose-dependent sedative effects on the central nervous system, including hypnotic, anticonvulsant, and hypothermic properties.³ However, it is known that there are optical isomers of linalool, and some reports showed the influence of chirality on physiological and psychological effects.⁴ (−)-Linalool led to increases in both physiological and behavioral arousal; in contrast, (−)-linalool showed the sedative effect. Then, the pharmacological evaluation of linalool should divide the linalool by optical isomers. Further, the pharmacological mechanism of (−)-linalool was not well understood, and there was no study focusing on the effect of (−)-linalool on the cerebral blood flow (CBF) of a human.

Arterial spin labeling (ASL) magnetic resonance imaging is a novel noninvasive technique that could measure CBF.

How to cite this article: Ota M, Sato N, Sone D, Ogura J, Kunugi H. (−)-Linalool influence on the cerebral blood flow in healthy male volunteers revealed by three-dimensional pseudo-continuous arterial spin labeling. Indian J Psychiatry 2017;59:225-7.
by taking advantage of arterial water as a freely diffusible tracer. In this study, we assessed the regional CBF changes before and after inhalation of (−)-linalool in healthy male volunteers by pseudo-continuous ASL (pCASL) to evaluate the effects of (−)-linalool on the brain function in an open-label trial.

MATERIALS AND METHODS

Subjects
Subjects were 15 healthy male adults (mean age; 31.0 ± 6.1 years). Participants who had no history of psychiatric illness or contact with psychiatric services were enrolled in the study. Participants were excluded if they had a prior medical history of central nervous system disease or severe head injury. They underwent the three-dimensional (3D)-pCASL just before and shortly after 10 min exposure to (−)-linalool. Written informed consent was obtained for the participation in the study from all volunteers, and the study was approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan.

Olfactory stimulation
(−)-Linalool was purchased from Sigma-Aldrich (St. Louis, MO, USA). For odor inhalation, 1.5 µl of the (−)-linalool (0.86 g/ml) was evaporated in a 7 m³ closed room at 25°C to use the linalool at the concentration of 0.03 ppm.[4] Participants were exposed to (−)-linalool for 10 min in this quiet room.

Magnetic resonance imaging data acquisition and processing
Experiments were performed on a 3-tesla MR system (Philips Medical Systems, Best, The Netherlands). The imaging parameters for all of the 3D-pCASL experiments were identical: single-shot gradient-echo echo planar imaging (EPI) in combination with parallel imaging (SENSE factor 2.0), FOV = 240 × 240, matrix = 80 × 80, voxel size = 3.0 mm × 3.0 mm, 52 slices acquired in the ascending order, slice thickness = 3 mm with no interslice gap, labeling duration = 1650 ms, postspin labeling delay = 1800 ms, TR = 5716 ms, TE = 20.5 ms, no time interval between consecutive slice acquisitions, radio frequency (RF) duration = 0.7 ms, pause between RF pulses = 0.7 ms, labeling pulse flip angle = 25°, bandwidth = 2.2 kHz/pixel, echo train length = 100. Four pairs of control/label images were acquired and averaged. The scan duration was 5:27. For measurement of the magnetization of arterial blood and also for segmentation purposes, an EPI M0 image was acquired separately with the same geometry and the same imaging parameters as the pCASL without labeling. Details of postprocessing of the ASL data are described elsewhere.[5] The individual CBF image contained some patchy noise, and thus a median filter (a nonlinear digital filtering technique) was used in this study. In median filtering, the neighboring pixels are ranked according to the intensity, and the median value becomes the new value for the central pixel. We used simple 2D median filtering (3 voxels × 3 voxels). The CBF maps were then normalized with the diffeomorphic anatomical registration using the exponentiated lie registration method using a template made from the average CBF maps of healthy individuals previously recorded at our center.[6] Each map was then spatially smoothed with a 6-mm full-width at half-maximum Gaussian kernel to decrease spatial noise and compensate for the inexactitude of normalization.

Statistical analysis
Statistical analyses were performed using SPM8 Software (London, UK). Differences of CBF between pre- and post-inhalation of (−)-linalool were assessed by paired t-test using the subjects’ age as nuisance variables. Only differences that met these criteria were deemed significant. In this case, a seed level of $P < 0.001$ (uncorrected) and a cluster level of $P < 0.05$ (uncorrected) were selected.

RESULTS

We evaluate the difference of CBF between pre- and post-inhalation of (−)-linalool using age as nuisance variables. There were significant CBF reductions in the right superior temporal gyrus to insula, anterior cingulate cortex (ACC), and posterior ACC after inhalation [Figure 1].

DISCUSSION

There were significant CBF reductions of healthy male volunteers in several brain regions after inhalation of (−)-linalool. To our knowledge, this is the first study focusing on the effect of (−)-linalool on the CBF in human.

Previous rodents study showed that linalool behaves as a competitive antagonist of $[^3]$H glutamate binding

Figure 1: Cerebral blood flow changes before and after the inhalation of (−)-linalool. There were significant cerebral blood flow reductions in superior temporal gyrus to insula and anterior cingulate cortex after the exposure to (−)-linalool.
and as a noncompetitive antagonist of [3H] dizocilpine binding in brain cortical membranes, pointing to a modulation of glutamatergic transmission.[7,8] Previous two studies using the positron emission tomography with [18F]-fluorodeoxyglucose showed the effect of lavender on the brain function in the human. One detected that lavender aroma activated the posterior part of the cingulate cortex, while suppression was found in the right superior temporal gyrus.[9] Another study detected the regional metabolic activation in the orbitofrontal, posterior cingulate gyrus, brainstem, thalamus, and cerebellum, as well as the reductions in the pre-/post-central gyrus and frontal eye field.[10] However, there was no clinical neuroimaging study about the effect of (−)-linalool.

The olfactory bulb is the first relay in the olfactory system; it comprises about 8000 glomeruli which receive the primary olfactory neuron axons.[11] The efferent glomeruli cells transmit the information of odor to the piriform cortex. The information processed in the piriform cortex then projects to various brain areas: orbitofrontal cortex, amygdala, hypothalamus, insula, entorhinal cortex, and hippocampus;[12] these areas are also involved in many emotional and cognitive functions.[13] We found the CBF reductions in right insula to superior temporal gyrus, anterior cingulate, dorsal anterior cingulate after the inhalation of (−)-linalool. The anterior cingulate cortex is related to cognitive attention.[14] The previous study showed that lavender had a negative effects on memory test performance.[15] The CBF reduction in the anterior cingulate gyrus would be due to the sedative effect of (−)-linalool. The present experiment revealed CBF reductions in the right superior temporal gyrus. Previous study reported that anxiety activated the anterior part of the temporal lobe.[16] Anxiety attack by lactate injection was reported to increase blood flow in the insula.[17] The glutamatergic pathway was thought to be related to anxiety,[18] and the CBF reduction in the present experiment supported emotional calming by (−)-linalool.

Limitations and directions for future research

We evaluate the effects of (−)-linalool in only male volunteers. In the ability of sensing odors, there was a gender difference.[19] They reported that women have a better sense of smell than men and retain the ability to smell longer than men. Further study with female individuals would bring the detailed information about the pharmacological mechanism of (−)-linalool.

CONCLUSIONS

We found the significant CBF reductions after inhalation of (−)-linalool. Our results indicated that the (−)-linalool showed the sedative effect, at least in part, through the olfactory pathway.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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