Role of Ventral Striatal Dopamine D1 Receptor in Cigarette Craving

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Background: Several theories of cigarette craving suggest that dopaminergic function in the ventral striatum plays an important role. The objective of this study was to determine correlations between craving-related brain activation and dopamine D1 receptor (D1R) binding in smokers.

Methods: Twelve smokers and 12 nonsmoking controls underwent [^{15}O]H_2O-positron emission tomography activation study and D1R-binding study using [^{11}C]SCH 23390, and the correlations between receptor binding and cue-induced regional cerebral blood flow (rCBF) changes were assessed. Consecutive D1R-binding changes were examined during a period of 6 months of postsmoking abstinence in five smokers.

Results: Cue-induced activation was observed in the left ventral striatum including the nucleus accumbens in smokers. D1R binding in the ventral striatum showed a negative relationship with cue-induced craving and rCBF changes. D1R binding was significantly low in smokers, and there was a trend of increase after smoking abstinence.

Conclusions: D1R binding and cue-induced rCBF changes in the ventral striatum suggest the important role of D1R in this region in cigarette craving.

Key Words: Dopamine D1 receptor, nicotine, PET, smoking, tobacco, ventral striatum

The major psychoactive component of tobacco, nicotine, has pharmacologic characteristics common to other drugs of abuse. It causes the desire to take the drug (craving), which contributes to the development and maintenance of drug dependence. The possible neurobiological mechanisms of craving for nicotine and other drugs of abuse have been discussed in relation to the conditioned aspects of the environment (Miyata and Yanagita 2001). However, nicotine is reported to produce its reinforcing and addictive properties by activating the dopaminergic pathway (Corrigall *et al.* 1992; Koob and Le Moal 1997; Rice and Cragg 2004; Zhang and Sulzer 2004; Zhou *et al.* 2001), but the regional molecular mechanism underlying cigarette craving has not been clarified fully. Long-term cigarette smoking may result in neuroadaptive changes at the synaptic level in craving-related regions that could be responsible for the conditioned responses to environmental stimuli (Cardinal and Everitt 2004; Koob and Le Moal 1997).

In an imaging study that used positron emission tomography (PET), smokers had greater increases in glucose metabolism in the paralimbic system in response to the cigarette cue than did nonsmoking controls (Brody *et al.* 2002). Likewise, in a functional MRI study of nicotine-deprived smokers, higher activation was observed in mesolimbic dopamine reward circuits after exposure to smoking-related images compared with neutral images (David *et al.* 2005; Due *et al.* 2002; McClernon *et al.* 2005). On the contrary, reduction of dopamine D1 receptor (D1R) binding in the ventral striatum was reported in cigarette smokers in a PET study (Dagher *et al.* 2001). These studies suggested that adaptive change of mesolimbic dopamine systems to chronic cigarette smoking contributed to the development of craving.

Recent multimodal studies of neuroreceptor imaging and activation study of alcoholic patients demonstrated the association between dopaminergic dysfunction and alcoholic cue-induced activation (Heinz *et al.* 2004, 2005). We planned a multimodal study to reveal the relationship between regional brain activation related to cigarette craving and regional D1R binding. Furthermore, D1R binding was examined successively to determine the effect of abstinence over 6 months.

Methods and Materials

Subjects

Twelve male subjects who smoked at least 15 cigarettes per day and who met the DSM-IV criteria for nicotine dependence participated in the PET activation study with [O^{15}]H_2O and in the D1R-binding study with [^{11}C]SCH23390 (mean age = 28.5 y, SD = 4.3; mean cigarettes per day = 25.4, SD = 8.9). Smoking severity was measured by the Fagerström Tolerance Questionnaire (FTQ; Fagerstrom 1978), and the mean score was 5.9 (SD = 2.0). Twelve male subjects who had never smoked cigarettes on a regular basis were recruited to serve as a comparison group (mean age = 25.3, SD = 4.3). All subjects were right-handed, as assessed by using the Edinburgh inventory (Oldfield 1971). The subjects were free of any criteria for mood, anxiety, or psychotic disorders or of a history of substance abuse or dependence other than nicotine, on the basis of unstructured psychiatric screening interviews. Subjects were also excluded if they were taking medication or had any history of or had a current medical condition that might affect the central nervous system at the time of scanning. Subjects with recreational alcohol or caffeine use not meeting the criteria for dependence were allowed to participate in the study but were instructed to abstain from these substances for 24 hours before scanning.

Subjects were examined by magnetic resonance imaging (MRI) to rule out brain diseases. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences (Chiba, Japan). After complete description

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of the study, written informed consent was obtained from all subjects.

Subject Preparation

Activation studies by smoking cues were performed on male smokers and nonsmokers by using [O^{15}]H_2O-PET. The smokers were asked to abstain from smoking for 24 hours before the scans, because withdrawal symptoms are reported to peak between 24 and 48 hours after beginning abstinence, and dropouts can be expected late during this period (Miyata and Yanagita 2001). Abstinence was confirmed by an undetectable plasma nicotine level. Within 2 weeks after the [O^{15}]H_2O-PET scan, another PET scan was performed to examine D1R binding by using [^{11}C]SCH 23390. None of the smokers stopped the habit of smoking after the [O^{15}]H_2O-PET scan, and they were allowed to smoke as per their usual habit until 30 min before the PET scan with [^{11}C]SCH 23390, because no difference in D1R binding was reported between the usual smoking state and overnight abstention (Dagher *et al.* 2001).

[O^{15}]H_2O-PET Activation Study

Each participant was scanned after the bolus intravenous administration of 10 mCi of [O^{15}]H_2O, 10 times at 10-min intervals in a single imaging session. Radioactivity was measured with Siemens ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN), which provides 63 planes and a 15.5-cm field of view. All emission scans were reconstructed with a Hanning filter cutoff frequency of .4 (full-width half-maximum [FWHM] = 7.5 mm). Ninety-second single-frame scans were initiated by the detection of head radioactivity and acquired in three-dimensional (3-D) mode.

The subjects were asked to watch a monitor placed 75 cm from their face, from 30 sec before the scan until the end of the scan. Smoking-related and neutral videos without soundtrack (Figure 1A) were used for stimulation. Smoking-related videos showed smoking men with cigarettes. Neutral videos matched the general content (objects, hands, and faces) and complexity without containing any smoking-related images. The videos were 2 min in length and started 30 sec in advance of the scan. The two videos, smoking related and neutral, were presented in an ABBAABBAAB design, and the order was balanced across the subjects. At the end of each PET scan, the subjects were asked "How much do you want to smoke a cigarette right now?", and the answers were given on a five-point scale (0–4), ranging from "not at all" to "extremely". The cue-induced craving score was calculated from the difference in average scores between presentations of smoking-related and neutral videos. After this self-rating of craving after each video, the subjects performed a Stroop task for 5 min as a distracter to minimize any cue-induced craving cross-talk between videos during the 10-min intervals of the PET scans (Garavan *et al.* 2000). The results of this Stroop task will be reported elsewhere.

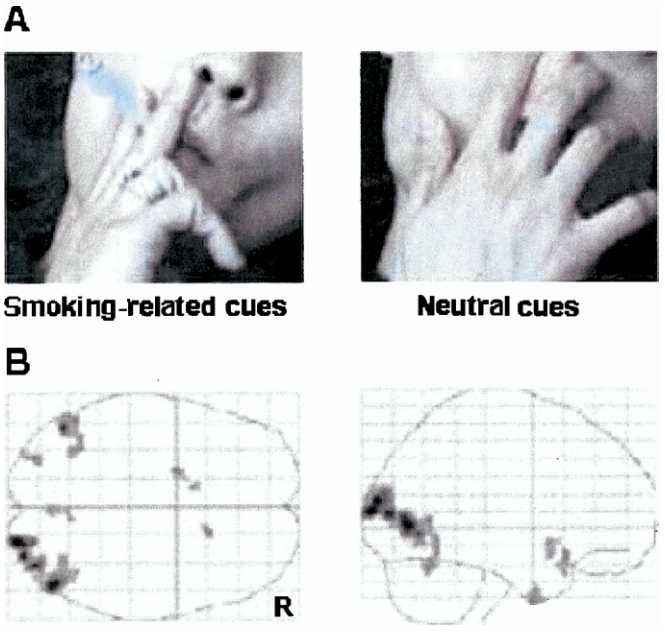

Figure 1. (**A**) Example of two stimulus images in the [O^{15}]H_2O activation study. (**B**) Regions with significant regional cerebral blood flow (rCBF) changes induced by smoking cues in 12 smokers. R = right. Transverse and sagittal glass brain views show voxels with significant brain activation ($p <$ .001, uncorrected).

Activation Data Analysis

Spatial preprocessing and statistical analysis were performed by the use of statistical parametric mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, England). All reconstructed images were realigned and transformed into a standard stereotactic anatomical space by using affine and nonlinear transformations. Spatially normalized images were smoothed by convolution with an isotropic Gaussian kernel to 8-mm FWHM. To remove the effect of variance as a result of global activity within and between subjects, global cerebral blood flow (CBF) of each subject was calculated as mean regional CBF (rCBF) over all intracerebral voxels. The adjusted rCBF of each subject for each voxel was generated by proportional scaling to a global CBF of 50. A voxel-based comparison of the adjusted rCBF values under the two conditions was performed in each group by using paired t tests. The resulting t values were transformed to z scores. Statistical test results with an uncorrected p level of $<.001$ were considered significant. Clusters of at least 25 contiguous significant voxels (voxel size = 2 × 2 × 2 mm) were interpreted as an activated region.

A possible relationship between significant alterations in rCBF and cue-induced smoking craving was estimated by Pearson's correlation coefficients for the sites identified in the comparison of the smoking-related and neutral video conditions. The adjusted mean regional activity was counted by averaging the values of the condition-specific adjusted rCBF for all voxels within the volume of interest (VOI) corresponding to the cluster composed of significant contiguous voxels in the comparison described above. Percentage changes in regional activity were calculated by the following formula: 100 × (smoking – neutral)/neutral, in which smoking was the adjusted mean regional radioactivity during presentation of the smoking-related video, and neutral was that during presentation of the neutral video.

As to the region in which we found a significant correlation only in one hemisphere, we delineated the spherical VOI with a 5-mm radius symmetrically on the other hemisphere by using the coordinates of pixel maxima as the centroid for the significant site, estimating rCBF changes and relation to the cue-induced craving scores. A p value of $<.05/n$ (n =number of comparisons) was used to test for statistical difference in the VOI analysis. In the statistical analysis of VOI data, the hypothesis of normality of data was confirmed by the Shapiro-Wilk normality test ($p > .05$)

To assess further association between cue-induced craving scores and brain activation elicited by cigarette versus control