

Effect of Modafinil on Cerebral Blood Flow in Narcolepsy Patients

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Background: To investigate the effects of modafinil on regional cerebral blood flow (rCBF) in narcolepsy, we performed ^{99m}Tc -ethylcysteinate dimer single photon emission computed tomography (SPECT) before and after modafinil or placebo medication.

Methods: Brain SPECT was performed twice during the awake state before and after modafinil or placebo administration for 4 weeks in 43 drug-naïve narcoleptics with cataplexy (M/F = 23/20, 29.5 ± 5.8 years). For SPM analysis, all SPECT images were spatially normalized to the standard SPECT template and then smoothed using a 12-mm full width at half-maximum Gaussian kernel. The paired *t*-test was used to compare pre- and post-modafinil or placebo SPECT images.

Results: The mean modafinil dose used was 207.8 ± 62.3 mg/day. Modafinil significantly reduced Epworth Sleepiness Scale scores from 20.3 ± 2.1 to 5.2 ± 3.1 ($P < 0.01$), while placebo did not. Compared to

the off-modafinil condition, the on-modafinil condition showed significantly increased rCBF in the right dorsolateral and bilateral medial prefrontal cortices. Conversely, after modafinil administration, rCBF was decreased in bilateral precentral gyri, left hippocampus, left fusiform gyrus, bilateral lingual gyri, and cerebellum.

There was no significant rCBF change after placebo administration.

Conclusion: By a chronic administration of modafinil in narcoleptic patients, rCBF increased in the bilateral prefrontal cortices, whereas it decreased in left mesio/basal, temporal, bilateral occipital areas, and cerebellum.

Keywords: Narcolepsy, modafinil, rCBF, SPECT, statistical parametric mapping

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NARCOLEPSY IS CHARACTERIZED BY EXCESSIVE DAYTIME SLEEPINESS (EDS), A DISRUPTION OF SLEEP-WAKE BEHAVIOR, CATAPLEXY (SUDDEN LOSS of muscle tone provoked by emotional stimuli), and the other REM sleep phenomena, such as sleep paralysis and hypnagogic hallucination.¹

Modafinil (a diphenylmethyl-sulfinyl-2-acetamide derivative) is a wake-promoting substance used for the treatment of hypersomnolence, particularly that associated with narcolepsy.² Modafinil is an increasingly popular medication due to its safety profile. Most side effects that have been reported are headache (if the modafinil dose was high or increased too quickly) and insomnia or nervousness, which are usually transient and dose dependent.³ Modafinil has multiple modes of actions. It activates $\alpha 1$ - and β adrenergic receptors,⁴ promotes glutamate excitatory transmission in the thalamus, hippocampus, and cortex,⁵ reduces GABA outflow via a monoamine-mediated mechanism,⁶ and activates serotonergic receptors.⁷ Although numerous animal studies have been performed, the mechanism whereby modafinil promotes wakefulness is still under investigation. Modafinil was found to increase extracellular dopamine levels, as determined by microdialysis in the rat nucleus accumbens and prefrontal cortex, as well as in the caudate of narcoleptic dogs.⁸ It was revealed that adminis-

tration of modafinil to rats produced wakefulness in association with activation of tuberomammillary nucleus and orexin neurons, two cell groups implicated in the control of normal wakefulness.⁹ Although the neurochemistry of this process remains obscure, it may involve histaminergic neurons in the tuberomammillary nucleus and hypocretin neurons in the perifornical area.^{5,9}

Modafinil is effective in maintaining wakefulness in narcolepsy patients, who have a hypocretin neuron deficit. Other studies have suggested that the cerebral cortex,¹⁰ thalamus,⁵ hippocampus,⁵ and periaqueductal gray matter¹¹ are also involved in the process of promoting wakefulness by modafinil.

The aim of the present study was to investigate regional cerebral blood flow (rCBF) changes in human narcolepsy patients who experienced a marked EDS improvement after modafinil administration. To achieve this, we performed ^{99m}Tc -ethylcysteinate dimer single photon emission computed tomography (SPECT) before and after modafinil or placebo administration in drug-naïve narcoleptics with cataplexy.

SUBJECTS AND METHOD

Subjects

We consecutively recruited 32 narcolepsy patients (M:F = 16:16, 14-47 years) for modafinil administration (modafinil-treated group) and 21 patients (M:F = 11:10, 15-42 years) for placebo administration (placebo-treated group). All patients suffered from narcolepsy with cataplexy and had no drug history for treatment of EDS or cataplexy. A clinical diagnosis of narcolepsy was made by a sleep specialist (SB Hong) based on an EDS >3 months and an unequivocal history of cataplexy, according to the revised International Classification of Sleep Disorders criteria for narcolepsy (ICSD-2).¹ The final diagnosis of narcolepsy was confirmed by sleep studies. Other information including the presence of sleep attacks, hypnagogic hallucina-

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tions, sleep paralysis, and a positive family history of narcolepsy were obtained from patients and their families.

Study Design

Before modafinil or placebo ingestion, all subjects underwent a physical examination, a routine blood test (hematology and chemistry panel including liver function tests), brain MRI, and baseline brain SPECT.

Each patient in modafinil group received modafinil 200 mg per day for 4 weeks. If a patient complained of an intolerable adverse event due to modafinil medication, (for example, headache, nervousness, or a hand tremor), the modafinil dose was reduced to 100-150 mg/day or divided into 2 dosages (100 mg in the morning and 100 mg at noon) to reduce symptoms. When a patient did not feel any EDS improvement, the modafinil daily dosage was increased to 300-400 mg/day.

Each patient in placebo group received one tablet a day of similar size and shape with modafinil, in the morning for 4 consecutive weeks. The placebo tablets were prepared independently by a hospital pharmacist.

Subjective EDS improvements were determined by Epworth Sleepiness Scale (ESS) percent decreases, defined as $([\text{pre-modafinil ESS} - \text{post-modafinil ESS}] \text{ or } [\text{pre-placebo ESS} - \text{post-placebo ESS}]/24) \times 100\%$. During the drug administration period, patients were examined by a physician every 2 weeks; blood testing for hematology and liver function was performed twice before medication was administered and again at the end of study period.

Overnight Polysomnography and Multiple Sleep Latency Test (MSLT)

The day before polysomnography, patients were asked not to drink alcohol or caffeinated beverages. Overnight polysomnography was recorded by Alice-3 system (Healthdyne, USA) and Compumedics S-series (Compumedics, Australia). Standard polysomnography consists of the 4-channel electroencephalogram (EEG, C3/A2; C4/A1; O1/A2; O2/A1), 4-channel electrooculogram (EOG), electromyogram (EMG) of submental, intercostal, and anterior tibialis muscles, and electrocardiogram with surface electrodes. Thermistor (for monitoring oronasal airflow), nasal air pressure monitor, oximetry (for oxygen saturation), piezoelectric bands (for thoracic and abdominal wall motion), and a body position sensor were also attached to the patients. Patients were recorded on videotape, using an infrared video camera, and were continuously observed by a polysomnography technician. Patients went to bed at 23:00 and were awakened at 07:00. Sleep architecture was scored in 30-sec epochs, and sleep staging was interpreted according to the standard criteria.¹¹ MSLT was performed using 4-channel EEG, 4-channel EOG, and single-channel EMG recordings by Alice-3 system (Healthdyne, USA) in the day following overnight polysomnography. MSLT consisted of 5 naps scheduled at 2-h intervals starting at 09:00. Patients were invited to lie down on a bed in a dark sound-attenuated room and instructed to try to fall asleep. Sleep latency was defined as the time elapsed from the start of the test (lights out) to the first 30-s epoch scored as sleep. Each sleep latency test was ended 20 min after the onset

of sleep or after 30 min of wakefulness. A sleep onset REM period (SOREMP) was defined as one or more epochs of REM sleep occurring within 15 min of the first 30-s epoch scored as sleep.

Final diagnosis of narcolepsy was determined based on clinical symptoms, overnight polysomnography, and MSLT by applying the criteria of narcolepsy.¹

^{99m}Tc-ethylcysteinate Dimer (^{99m}Tc-ECD) Brain SPECT

^{99m}Tc-ECD was injected intravenously for the SPECT studies. A brain SPECT scan was performed within 30 to 60 min of radiotracer injection (25mCi) using a 3-headed Triad XLT system equipped with low-energy and high-resolution collimators (Trionix Research Laboratory, Twinsburg, OH, USA). The transaxial system resolution of this camera was 6.9 mm full width at half maximum. Images were reconstructed by filtered back-projection using a Butterworth filter. Attenuation correction was performed using Chang's method (attenuation coefficient = 0.12 cm⁻¹).¹² The SPECT voxel dimension was 3.56 × 3.56 × 3.56 mm (x, y, z). SPECT studies were performed before narcolepsy treatment commenced. All participants were asked to refrain from caffeinated beverages but were allowed to drink water from 07:00 until the end of the SPECT study. Before radiotracer administration, patients had a nap (15-20 min) if sleepy, but were instructed not to fall asleep after the ECD injection. Wakefulness after the ECD injection was monitored using 4-channel EEG, 2-channel EOG, and single-channel EMG recordings. Informed consent was obtained from all patients after the study protocol, SPECT study procedure, and potential hazards associated with radioisotope injection had been explained. The Institutional Review Board at Samsung Medical Center authorized the informed consent form and the study protocol, which included the administration of a radioactive substance and SPECT scanning.

SPM Analyses of Brain SPECT Images Obtained Before Versus After Modafinil or Placebo Administration, and on-Modafinil Versus on-Placebo Conditions

Pre- and post-modafinil or placebo SPECT images were manipulated using MATLAB 6.3 (The MathWorks, Natick, MA) incorporated into SPM 2 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, University of London, UK). Raw SPECT images (interfile 3.0 format) were converted to Analyze format. Before the spatial normalization of pre- and post-modafinil or placebo SPECT images using a standard SPECT template, post-modafinil or placebo SPECT images were realigned to pre-modafinil or placebo SPECT images for each subject, and realigned matrixes and subject mean images were saved. Using these realignment processes, all post-modafinil or placebo SPECT images were correctly registered to pre-modafinil or placebo SPECT images. Mean images were spatially normalized into a standard SPECT template using a 12-parameter affine transformation and a nonlinear transformation, and the normalization parameters of each subject mean image were then adjusted to realigned pre- and post-modafinil or placebo SPECT images of same subjects. The accuracy of the spatial normalization was checked using a cross-registra-

Table 1—Patients' Characteristics

	Modafinil treated group (<i>n</i> = 32)	Placebo treated group (<i>n</i> = 21)	P
M : F	16 : 16	10 : 12	0.469
Mean age, yr	31.4 ± 12.3	29.1 ± 9.9	0.490
EDS onset age, yr	17.9 ± 4.9	17.6 ± 5.1	0.814
Cataplexy onset age, yr	20.5 ± 5.5	19.6 ± 5.1	0.533
Mean ESS	17.2 ± 3.5	16.0 ± 3.9	0.252
Mean SSS	4.3 ± 1.9	4.4 ± 2.0	0.762
HH/SP, number	23/19	17/15	0.754/0.842
Overnight polysomnography			
Mean sleep latency, min	7.6 ± 3.8	6.4 ± 3.5	0.264
Mean REM sleep latency, min	50.0 ± 46.8	60.7 ± 44.1	0.408
Mean AHI, per hour	1.7 ± 1.6	1.6 ± 1.7	0.882
Mean arousal index, per hour	13.7 ± 5.5	11.5 ± 4.5	0.114
Multiple Sleep Latency Test			
Mean sleep latency, min	3.8 ± 2.9	4.6 ± 2.8	0.299
Sleep-onset REM periods, number	3.7 ± 1.3	3.7 ± 1.2	0.975
Mean REM sleep latency, min	2.6 ± 2.3	2.9 ± 2.6	0.675

ESS, Epworth Sleepiness Scale; SSS, Stanford Sleepiness Scale; HH, hypnagogic hallucination; SP, sleep paralysis; REM, rapid eye movement; Independent *t*-test, *P* < 0.05, #Chi-square test, only in case of M:F and HH/SP, number, *P* < 0.05.

tion function. Spatially normalized images were then smoothed by convolution using an isotropic Gaussian kernel with a 14-mm full width at half maximum to increase the signal to noise ratio.^{13,14} Scaling of counts was based on normalization of white matter counts across the study conditions.

Normalization that includes white and gray matter voxels would be problematic. Because white matter is known to be less affected by the experimental effect or disease condition,¹⁵ the level of rCBF in whole brain was normalized with the mean count of white matter. Moreover, no experimental data were demonstrated that white matter is mainly affected by modafinil. After normalization, post hoc paired comparisons were performed between on- and off-modafinil or placebo administration. The group comparisons between off-modafinil and off-placebo and on-modafinil and on-placebo administrations were performed using unpaired *t*-test. To test the prior hypothesis that modafinil improves the prefrontal function,¹⁶ a small volume correction (SVC) was made in these areas. We applied the corrections on volumes of interest centered on the coordinates and the results of increased rCBF with small volume correction (sphere with 50 mm radius, center point: *x*, *y*, *z* = 0, 36, 16). The height threshold was set at an uncorrected *P* < 0.001 and the extended threshold to *kE* > 50.¹⁷ The results were superimposed on the 2-D planes of a single patient's MRI template after spatial normalization.

RESULTS

Patient Characteristics (Table 1)

All 53 patients (modafinil-treated group, *N* = 32, placebo-treated group, *N* = 21) had EDS, sleep attacks, and cataplexy. The mean ESS of patients and their mean Stanford Sleepiness Scale (SSS) suggest moderate to severe EDS.

Detailed clinical information as well as overnight polysomnography and MSLT findings are listed in Table 1.

Wakefulness Monitoring During SPECT Study

EEG, EOG, and EMG were monitored during SPECT studies to measure the duration of wakefulness after ECD injection.

Before modafinil or placebo administration, mean sleep latency after an ECD injection for SPECT study was 6.24 ± 3.4 min (range 3–10.5). After modafinil or placebo administration, the mean sleep latency was 10.7 ± 2.8 min (range 6–15) in modafinil-treated group (paired *t*-test, *P* < 0.001) and 5.9 ± 3.2 (range 3.5–9.0) in placebo-treated group (*P* = 0.212).

Modafinil or Placebo Effect on Excessive Daytime Sleepiness

Modafinil administration decreased ESS from 20.3 ± 2.1 to 5.2 ± 3.1 (*P* < 0.01), which suggests that modafinil markedly improves EDS. After 2 weeks of modafinil at 200 mg/day, 6 patients (18.7%, 6/32) did not feel any subjective EDS improvement (ESS decrease, 0% to 25%). Thus, the daily modafinil dosage was increased to 250–400 mg/day in those patients until they felt satisfactory improvement of EDS. However, ESS and SSS were not changed significantly after 4 weeks placebo administration (18.4 ± 3.9 → 16.3 ± 2.7 in ESS; 4.4 ± 2.1 → 4.5 ± 1.9 in SSS, Wilcoxon signed rank test, *P* > 0.05).

Summarizing, most patients experienced the disappearance or a significant subjective improvement of EDS (mean ESS decrease, 69.9% ± 12.5%) on modafinil (207.8 ± 62.3 mg/day).

Modafinil Dosage and Adverse Effects

After receiving modafinil medication, 10 patients (31.2%, 10/32) experienced a mild headache for several days (mean 4.2 ± 2.2 days, range 1–9) but this disappeared despite continuous medication at the same dosage. Five patients (15.6%, 5/32) suffered hand tremors or nervousness, and dosage was reduced in these patients to 100 or 150 mg. No serious adverse event occurred with modafinil. Patients receiving placebo had no adverse events.

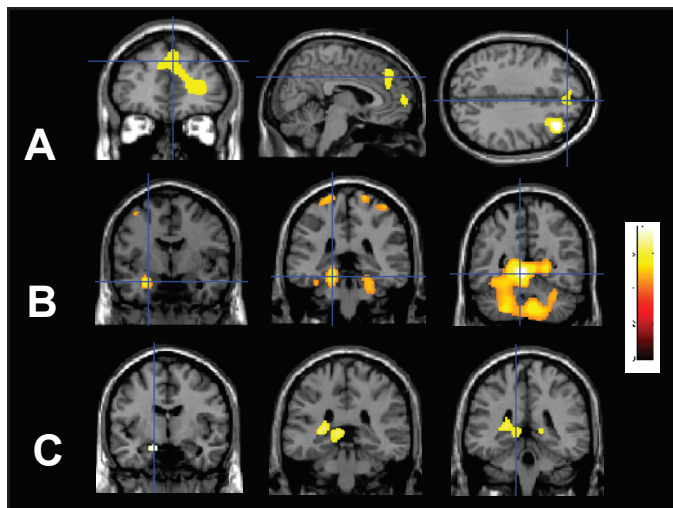


Figure 1—SPM results demonstrating brain regions with rCBF increase or decrease after modafinil administration in narcolepsy patients.

(A) According to SPM overlaid on T1 MR images, modafinil administration increased rCBF in bilateral medial prefrontal cortices, right dorsolateral prefrontal cortex at an uncorrected $P < 0.001$.

(B) Modafinil administration decreased rCBF in left hippocampus (left), bilateral precentral gyri, left fusiform gyrus (middle) and bilateral lingual gyri and cerebellum (right) in the anterior to posterior direction in coronal MR images at an uncorrected $P < 0.001$. The result at FDR corrected $P < 0.05$ is very similar to this figure.

(C) Compared to the on-placebo condition in placebo group, the on-modafinil condition in modafinil group showed rCBF decrease in left hippocampus (left) and bilateral parahippocampal gyri (middle and right)(uncorrected $P < 0.05$).

*The left-hand side of the images represent the left side of the brain.

SPM Analysis of ^{99m}Tc -ECD SPECT

1) Modafinil Group (N = 32), On-modafinil Vs. Off-modafinil (Table 2)

Compared to the off-modafinil condition, the on-modafinil condition showed significantly increased rCBF in the right dorsolateral and bilateral medial prefrontal cortices ($P < 0.001$, uncorrected; Figure 1 A). In the SVC analysis for the prefrontal cortices,¹⁷ the rCBF was also significantly increased in the same brain regions at the level of false discovery rate (FDR) corrected $P < 0.05$. On the other hand, after modafinil administration, rCBF was decreased in bilateral precentral gyri, left hippocampus, left fusiform gyrus, bilateral lingual gyri, and vermis of cerebellum (uncorrected $P < 0.001$, FDR corrected $P < 0.05$; Figure 1B).

2) Placebo Group (N = 21), On-placebo Vs. Off-placebo

The on-placebo condition showed no significant rCBF change (neither increase nor decrease of rCBF) compared to the off-placebo condition.

3) Off-modafinil (N = 32) Vs. Off-placebo Group (N = 21)

There were no significant rCBF differences between off-modafinil and off-placebo groups both at the level of uncorrected $P < 0.05$ or FDR corrected $P < 0.05$.

4) On-modafinil (N = 32) Vs. On-placebo Group (N = 21)

Compared to the on-placebo condition in placebo group, the on-modafinil condition in modafinil group showed significant reduced rCBF in the left hippocampus ($x:y:z = -16: -4: -22$, $T = 2.84$, $z = 2.64$, $P = 0.004$) and left ($x:y:z = -14: -39:3$, $T = 2.86$, $z = 2.66$, $P = 0.004$) and right ($x:y:z = 16: -38:4$, $T = 2.84$, $z = 2.64$, $P = 0.004$) parahippocampal gyri (independent t -test) (Figure 1C).

DISCUSSION

In the present study, we sought to examine the effects of modafinil on rCBF throughout the whole brain in drug naive narcolepsy patients.

After modafinil administration, rCBF increased in the bilateral prefrontal cortices, whereas rCBF decreased in the hippocampus, fusiform-lingual gyri, and cerebellum.

CBF Increase in Prefrontal Cortex after Modafinil Administration

Medial prefrontal cortex (MPF) and dorsolateral prefrontal cortex (DLPF) are known to display distinct patterns of activations during cognitive tasks (wakefulness) and during sleep.¹⁸⁻²² In non-sleep deprived normal young adults, rCBF of MPF was negatively correlated with delta power values measured at the central scalp locations during NREM sleep.¹⁸ The brain activities in the parts of DLPF (inferior and middle frontal gyri) were significantly diminished during REM sleep.²⁰ The relative hypoactivity of the prefrontal cortex during REM sleep may explain the characteristic lack of insight, the alteration of time perception or even the delusional belief of being awake during dreaming.²⁰ Normally MPF and DLPF are known to be activated in resting condition during wakefulness compared to slow wave sleep or REM sleep.^{21,22}

MPF as well as anterior cingulate is primarily involved in attention and working memory in combination with the DLPF.^{23,24}

Working memory disturbances have been reported in as many as 40% to 50% of narcoleptic patients.²⁵ One study found mild verbal memory problems in narcoleptics, which were mainly due to deficient perceptual encoding.²⁶ However, other researchers showed the intact short- and long-term memory in narcoleptics on standardized neuropsychological tests.²⁷ Attention and memory are closely related; thus a person with attention impairment frequently complains of memory decline rather than of attention difficulty. Deficits in vigilance may cause attention fluctuation in narcoleptics, particularly during long and repetitive tasks.^{28,28}

It is not clear that modafinil improves working memory and executive function in our narcolepsy patients in this study because neuropsychological tests were not performed before and after modafinil treatments. However, our results suggest that a chronic modafinil administration affects the rCBF of MPF and DLPF in narcoleptic brains.

Why Did Modafinil Reduce CBF of Multiple Brain Regions?

After modafinil administration, cerebral perfusion was reduced in hippocampus, fusiform and lingual gyri and cerebellum in the present study. Comparison between on-modafinil condition

Table 2—SPM Results Showing MNI Coordinates and Significance Levels of Brain Regions with rCBF Increase or Decrease after Modafinil Administration in Narcolepsy Patients

Location	Side	Coordinates (mm)			Z	T	FDR corrected P	Uncorrected P
		x	y	z				
rCBF increase								
Medial prefrontal cortex	L	-4	58	8	3.7	4.46	0.024*	0.00011
	R	4	40	44	3.2	3.75	0.024*	0.00009
Dorsolateral prefrontal cortex	R	36	30	36	4.2	5.48	0.024*	0.00001
rCBF decrease								
Precentral gyrus	L	-40	-18	64	3.6	4.35	0.026	0.00014
	R	18	-34	76	3.6	4.32	0.027	0.00015
Hippocampus	L	-30	-4	-20	4	4.92	0.013	0.000036
Fusiform gyrus	L	-20	-34	-16	4.4	5.64	0.006	0.00025
Lingual gyrus	L	-8	-54	-6	5.2	7.55	0.003	0.0000001
	R	24	-46	4	5	7	0.003	0.0000003
Cerebellum (vermis/uvula)	B	0	-64	-30	4.7	6.38	0.004	0.0000013

L:left, R:right, B:both, FDR: false discovery rate, *MNI (Montreal Neurological Institute) coordinate. *: Small volume corrected (SVC) FDR *P* (sphere with 50mm radius, center point: x, y, z = 0, 36, 16).

and on-placebo condition showed that modafinil treated group showed the CBF decrease in bilateral parahippocampal gyri adjacent to hippocampus. As presented, the brain regions showing CBF decrease were slightly different between the findings of off- and on-modafinil group and that of on-modafinil and on-placebo groups. Different statistical methods (paired *t*-test vs. independent *t*-test) and individual variations of baseline CBF²⁹ in 2 different subject groups (modafinil-treated vs. placebo-treated group) may produce similar not the same compared to the paired comparison between the same subjects before and after drug administration.

Various receptors of GABA, an inhibitory neurotransmitter, exist in temporal lobe including hippocampus and extratemporal neocortex.³⁰ The posterior lobe of cerebellum is involved in the fine motor coordination via the inhibition of involuntary movement using GABA. Modafinil showed the neuroprotective effect in the movement-related behavior, locomotor activity, hand-eye coordination, and small fast movements in an animal model of Parkinson disease.³¹ It was reported that the wakefulness produced by modafinil was related to a reduction in GABA release in several brain regions.³²

Although there was no evidence that mesio-basal temporal areas and cerebellum showing reduced rCBF play the role in the wake-promotion, modafinil significantly reduced rCBF in the GABA-related temporal lobe and cerebellum as well as improved the vigilance of our narcoleptic patients (ESS, 20.3 ± 2.1 → 5.2 ± 3.1) in the present study. Nevertheless, the reason why modafinil reduces rCBF in several regions of narcoleptic brains remains unclear.

Modafinil Effect on rCBF in Narcolepsy Patients Versus Healthy Volunteers

There are quite a few conflicting reports concerning the locus of modafinil effect. In previous animal study, administration of modafinil induced marked Fos labeling in neurons of the anterior hypothalamic nucleus and adjacent areas that were considered to be wake-promoting areas.³³

We recently performed a SPECT study to investigate the effects of modafinil on rCBF in normal subjects (in press). This study showed that a single dose of modafinil (400 mg at once) increased rCBF mainly in thalamus and pons as well as prefrontal and cingulate cortices in healthy volunteers. There were no brain areas showing reduced rCBF by modafinil as well as placebo administration. In the present study, we observed that chronic modafinil treatment for 4 weeks produced both rCBF increase (in right dorsolateral and anterior cingulate cortices) and rCBF decrease (in bilateral fronto-temporal cortices and cerebellum).

To our knowledge, there has been no SPECT study of rCBF changes in long-term administrations of modafinil in either narcolepsy patients or healthy volunteers. The applicability of the short-term effects to chronic drug therapy is very limited because there are known changes in the rate of metabolism, drug-induced changes in receptor density or efficiency of receptor coupling, and sensitization in chronic drug therapy. Thus short-term effect of modafinil administration may be different from the effect of a long-term administration.

Modafinil modulated the blood flow of the thalamus and pons in our previous work, but we could not find rCBF changes in those areas in this study. Moreover, we administered single dose of modafinil 400 mg at once to normal subjects in our previous study whereas the average modafinil dose was 207.8 mg a day administered to narcolepsy patients in the present study. Only modafinil-treated patients showed the improvement of EDS by ESS and prolonged sleep latency during SPECT studies. It seems that long-term modafinil administration produces clinically beneficial effects on narcolepsy patients through the top down control circuitry involved in attention and executive functions, although a task-activation study was not performed before and after modafinil administration in our patients.

Our previous FDG-PET and SPECT studies showed definite hypometabolism or hypoperfusion of the hypothalamus and thalamus in drug-naïve narcoleptics.^{13,14} Thus, a small increase in rCBF by modafinil in the hypothalamus may have been missed by SPECT, due to its lack of sensitivity.

CONCLUSION

This study is the first to investigate the effects of modafinil on rCBF in drug-naïve narcoleptics with cataplexy. The present study demonstrates that the dose of modafinil that induces a satisfactory wakefulness-promoting response in human narcoleptics also causes regional increase in cerebral blood flow in the bilateral prefrontal cortices.

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