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Methylphenidate's Effect on Cerebral Blood Flow in Patients with Narcolepsy

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We performed ^{99m}Tc-ethyl cysteinate dimer brain single-photon emission computed tomography before and after administering methylphenidate, for four weeks, to narcolepsy patients with cataplexy. Cerebral blood flow increased in the bilateral cingulate gyri and both thalami with methylphenidate treatment as compared to pre-methylphenidate treatment. methylphenidate treatment also produced an regional cerebral blood flow increase in the bilateral nucleus accumbens, cingulate gyri, superior frontal gyri, and bilateral amygdalo-hippocampi and parahippocampal gyri as compared to pre-methylphenidate treatment. Moreover, no brain region showed a significant regional cerebral blood flow decrease after methylphenidate treatment. **Sleep Med Res 2010;1:30-31**

Key Words Narcolepsy, Methylphenidate, Cerebral blood flow.

Methylphenidate (MPHE) is one of the most commonly prescribed stimulants for treatment of excessive daytime sleepiness in narcolepsy patients.[1] No prior studies have investigated MPHE-induced regional cerebral blood flow (rCBF) changes in narcolepsy patients. Therefore, our present study aimed to compare rCBF, using a voxel-based analysis with statistical parametric mapping (SPM), before and after narcolepsy patients received MPHE. We performed brain single-photon emission computed tomography (SPECT) on each of 18 drug-naïve narcoleptics with cataplexy (M/F = 10/8, mean age 27.5 ± 3.9 years). Patients underwent brain SPECT during their awake state, twice before, and twice after receiving 4 weeks' MPHE treatment. For the SPM analysis, we spatially normalized all SPECT images to the standard SPECT template and smoothed them using a 12-mm full width at half-maximum Gaussian kernel. To compare pre- and post-MPHE SPECT images, we used the paired t-test. The mean MPHE dose was 13.6 ± 4.8 mg/day. MPHE significantly reduced patients' Epworth Sleepiness Scale (ESS) scores, from 20.3 ± 2.1 to 11.3 ± 4.6 ($p < 0.01$).

In our SPM analysis, MPHE treatment showed rCBF increased in the bilateral nucleus accumbens, cingulate gyri, superior frontal gyri, and bilateral amygdalo-hippocampi and parahippocampal gyri, as compared to in the pre-MPHE treatment (uncorrected $p < 0.001$). The left side of each image represents the left hemisphere of the brain. Scales in the colored bar are t-scores (Fig. 1).

When we administered MPHE to the narcoleptic patients, rCBF increased in their bilateral medial and dorsolateral frontal cortices and bilateral medial and lateral temporal areas. No brain region showed a significant rCBF decrease after MPHE treatment. We have previously reported modafinil's effect on rCBF in narcolepsy patients. After modafinil treatment, rCBF increased in their bilateral prefrontal cortices, but it decreased in the left mesio/basal, temporal, and bilateral occipital areas and the cerebellum.[2] Thus, both MPHE and modafinil affected the rCBF in the medial and dorsolateral prefrontal cortices in narcoleptic brains. Working memory disturbances have been reported in as many as 40% to 50% of narcoleptic patients and deficits in vigilance may cause attention fluctuation in narcoleptics, particularly during long and

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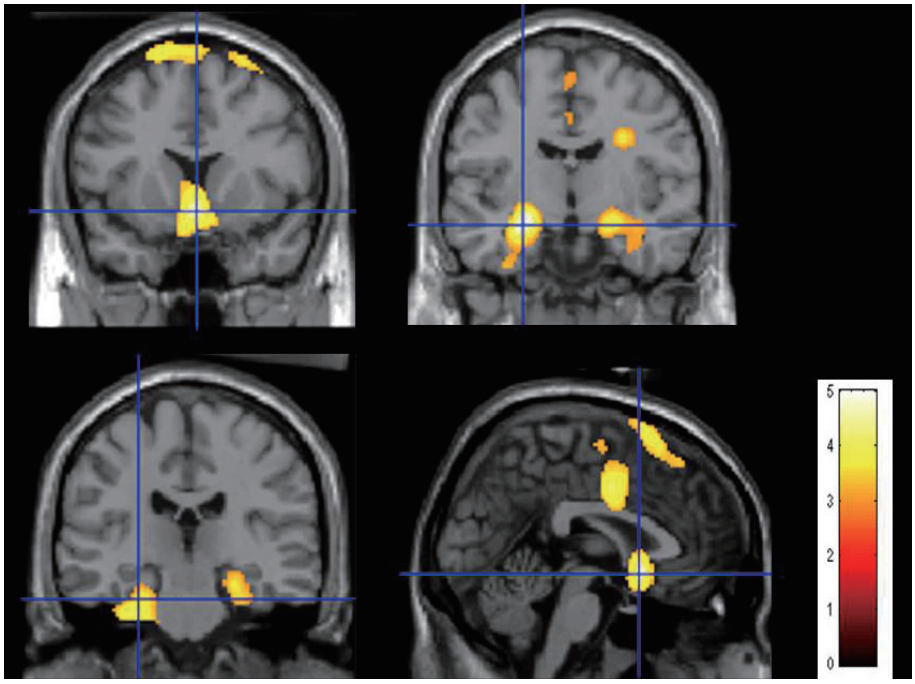

Fig. 1. SPM results demonstrating brain regions with increased rCBF after methylphenidate treatment of narcolepsy patients. According to the SPM, overlaid on T1 MR images, methylphenidate treatment increased rCBF in the bilateral prefrontal and temporal cortices. SPM: statistical parametric mapping, rCBF: regional cerebral blood flow.

repetitive tasks.[3,4] These SPECT findings suggested that two stimulants may be related to improve memory disturbances although neuropsychological tests were not performed before and after stimulant treatments. Various receptors for gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, exist in the temporal lobe, including in the hippocampus and extratemporal neocortex.[5] Although, in the present study, we found no evidence the mesio-lateral temporal area plays a role in wake promotion, MPHE significantly increased rCBF in the GABA-related temporal lobe and improved our narcoleptic patients' vigilance (ESS scores 20.3 → 11.3). This study is the first to investigate MPHE's effect on rCBF in drug-naive narcoleptics with cataplexy. Our study demonstrates that, in human narcolepsy, the drug MPHE causes an rCBF increase in the bilateral prefrontal and temporal cortices.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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