High-Frequency Repetitive Transcranial Magnetic Stimulation Decreases Cigarette Smoking

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Background: The mesolimbic dopaminergic reward system seems to play a crucial role in reinforcing effects of nicotine. Recently, acute high-frequency repetitive transcranial magnetic stimulation (rTMS) of frontal brain regions has been shown to efficiently modulate the mesostriatal and mesolimbic dopaminergic system in both animals and humans. For this reason, we investigated whether high-frequency rTMS would be able to influence nicotine-related behavior by studying rTMS effects on craving and cigarette smoking.

Method: Fourteen treatment-seeking smokers were included in a double-blind crossover trial, conducted in 2002, comparing single days of active versus sham stimulation. Outcome measures were rTMS effects on number of cigarettes smoked during an ad libitum smoking period and effects on craving after a period of acute abstinence.

Results: High-frequency (20-Hz) rTMS of left dorsolateral prefrontal cortex reduced cigarette smoking significantly ($p < .01$) in an active stimulation compared with sham stimulation. Levels of craving did not change significantly.

Conclusion: High-frequency rTMS may be useful for treatment in smoking cessation.

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Repetitive transcranial magnetic stimulation (rTMS) is a new technique that has been found to be useful as a potential treatment for neuropsychiatric diseases.[1] With regard to the neurobiological mechanisms involved, there is compelling evidence that rTMS causes changes in neuronal circuits. Such alterations include selected local modifications in the dynamic release patterns of biogenic amines and amino acids.[2] Using intracerebral microdialysis in rodents, stimulation of dopamine release could be demonstrated in the dorsal hippocampus as well as in the shell of the nucleus accumbens.[3] These data provide compelling in vivo evidence that acute high-frequency rTMS of frontal brain regions has a modulatory effect on both the mesolimbic and the mesostriatal dopaminergic systems. Moreover, these findings are fairly compatible with data showing that high-frequency rTMS of the human prefrontal cortex induces dopamine release in the caudate nucleus.[4] For this reason, high-frequency rTMS is considered to be especially useful in neuropsychiatric disorders associated with subcortical dopamine dysfunction.[2–4]

The primary subjective and physiologic effects of smoking are known to result from the central actions of nicotine.[5,6] In this context, the mesolimbic dopaminergic reward system seems to play a pivotal role in reinforcing effects of nicotine.[6,7] Decreased function in brain reward systems during nicotine withdrawal seems to be closely associated with craving, relapse, and continued nicotine consumption.[8] For this reason, modulation of dopaminergic neurotransmission might serve as a potential target for treating tobacco addiction. Additional support for this hypothesis comes from studies with bupropion, an atypical antidepressant blocking neuronal uptake of dopamine, which has recently been approved as a treatment for smoking cessation.[9,10]

Considering that high-frequency rTMS has been shown to alter dopaminergic neurotransmission in subcortical structures, we investigated whether 20-Hz rTMS is able to reduce cigarette smoking and craving.

METHOD

Probands

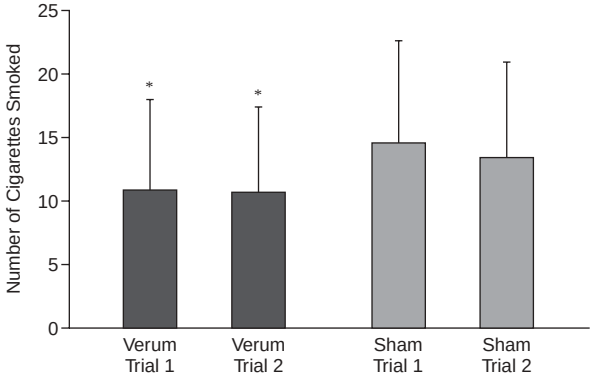
Fourteen right-handed probands who wished to quit smoking were recruited through advertisement in 2002.

Table 1. Baseline Demographics and Smoking Characteristics of 14 Treatment-Seeking Probands[a]

Variable	Value
General characteristics	
Age, y (range, 23–55)	35.4 ± 8.9
Education level, y	11.2 ± 3.6
Race, % white	100
Gender, M/F, N	2/12
Smoking characteristics	
Cigarettes per day	16.8 ± 10
Smoking duration, y	16.7 ± 10.1
No. of serious attempts to quit smoking	3.2 ± 2.6
FTND score	5.1 ± 1.9

[a]Values shown as mean ± SD unless otherwise noted.
Abbreviation: FTND = Fagerström Test for Nicotine Dependence.

Figure 1. Effect of High-Frequency Repetitive Transcranial Magnetic Stimulation on the Number of Cigarettes Smoked (mean ± SD) During an Ad Libitum Smoking Phase of 6 Hours



*Denotes significant difference from sham stimulation ($p < .01$).

Subjects were regular cigarette smokers (12 female, 2 male) aged 23 to 55 years. Smoking characteristics (Table 1) were comparable to those reported in other studies investigating therapeutics for nicotine addiction.[11] All candidates received a structured clinical interview combined with a short physical examination and completed several questionnaires, including the Fagerström Test of Nicotine Dependence (FTND)[11] as well as a drug and health history questionnaire. Standard cut-off thresholds were used to eliminate those persons with significant current or past alcohol, drug, or psychiatric symptomatology.[12] Subjects were also excluded for positive urine toxicology (cocaine, opiates, amphetamines, benzodiazepines). All candidates abstained from smoking 12 hours before each rTMS session and gave written informed consent to take part in the study, which was approved by the local ethics committee.

Study Design

Within a crossover design, each subject received 2 trials of active and 2 trials of sham stimulation in a randomized order on 4 consecutive days. Patients and clinical staff were unaware of stimulation condition. On each study day, sessions started in the early afternoon (1 p.m.). The participants received 20 trains of rTMS at a rate of 20 Hz for 2.5 seconds over 14 minutes (1000 pulses/session; intertrain interval: 42.5 seconds) by means of a repetitive magnetic stimulator (Magstim Co., Whitland, Dyfed, U.K.). Stimulation site was the left dorsolateral prefrontal cortex, defined as 5 cm anterior and in a parasagittal plane from the point of maximum stimulation of the abductor pollicis muscle. Stimulation intensity was at 90% of motor threshold. Sham stimulation was given at the same location and frequency by using a sham-coil system (Magstim, U.K.). The stimulation paradigm was identical with stimulation conditions leading to a marked dopamine release in mesolimbic structures such as the nucleus accumbens.[2,3]

Ratings

Two outcome measures were used. Craving was measured with a 10-cm–long, 100-point visual analogue scale administered at baseline and 30 minutes after rTMS treatment. Using this scale, the subjective state "desire to smoke" was assessed, as it has been done earlier in a study on naltrexone alteration of acute smoking response.[13] "Desire to smoke" ratings have been shown to be sensitive to assess self-reported levels of craving.[14] Number of cigarettes smoked was noted during an ad libitum smoking phase (6-hour period) after rTMS treatment. The subjects were instructed to smoke freely using their own chosen brand of cigarettes. Data were obtained under natural conditions in the subjects' normal living or working environment, not under laboratory conditions, since environmental and other contextual factors have been shown to decisively influence individual smoking behavior.[15] For this reason, subjects had to keep a daily diary 3 weeks before entering the study in order to check compliance and accurate assessment of numbers of cigarettes smoked.

Statistical Analysis

Each subject participated in several trials, so we expected a repeated-measures covariance structure of the data. Instead of the more traditional repeated-measures analysis of variance, we used a linear mixed-effects model for data analysis. This class of statistical models allows for more flexibility in model construction and selection.[16] In this context, using this linear mixed-effects model enabled us to judge whether an order effect of stimulation conditions (active stimulation/sham stimulation) should be included in the model, on the basis of objective statistical criteria. The threshold for significance was set at $p < .05$.

RESULTS

Using a linear mixed-effects model for data analysis, group membership (active vs. sham stimulation) was the

fixed-effect covariate and subject ID was included as a random-effect covariate.

The fixed group effect was found to be significant ($p < .01$) for "number of cigarettes smoked" (95% CI = 1.301 to 5.109) but not for "craving." The direction of the effect indicated that the number of cigarettes smoked was significantly smaller under active stimulation conditions compared with sham stimulation conditions (Figure 1).

Other than complaints of mild headache in 2 cases after active stimulation, patients tolerated rTMS without difficulty.

DISCUSSION

The present study implies that high-frequency rTMS may reduce cigarette smoking. In contrast, levels of craving did not change significantly. The failure to find rTMS effects on craving should not be misinterpreted as having shown that rTMS does not alter craving. It might be due to methodological issues such as the assessment of craving, focusing on subject's desire to smoke, the rating scale being less sensitive than the cigarette count, or the actual sample size being too small to show statistically significant effects.

The mechanism of action of high-frequency rTMS in cigarette smokers is an object of speculation but may be similar to that of some drugs used to treat smokers. Bupropion is supposed to act by mimicking nicotine's actions on brain reward systems by blocking neuronal uptake of dopamine.[6] An identical mechanism might account for the action of high-frequency rTMS, since selective dopamine release in subcortical structures could be demonstrated after rTMS both in animals[2,3] and humans.[4] Especially, immediate marked release of dopamine after prefrontal high-frequency rTMS, as indicated by raclopride positron emission tomography,[4] may closely resemble pronounced catecholamine-releasing effects preferentially resulting from fast forms of nicotine delivery such as cigarette smoking.[17] Moreover, high-frequency rTMS has been shown to influence an array of neurotransmitters and biogenic amines including arginine vasopressin[2] and serotonin (5-HT),[18] which are also altered by nicotine.[19] In particular, tobacco smoking is associated with reductions in hippocampal serotonin,[20] which may be corrected by rTMS-induced increase in hippocampal 5-HT concentrations.[18] These biological qualities of high-frequency rTMS may explain why even daily sessions of active rTMS were able to reduce cigarette smoking, whereas acute doses of bupropion failed to reduce smoking.[12]

Our data obtained in a small number of cigarette smokers need to be confirmed, but the results of this pilot study support further investigation of high-frequency rTMS for treatment in smoking cessation.

Drug names: bupropion (Zyban and others), naltrexone (ReVia and others).

REFERENCES

1. Sachdev PS, McBride R, Loo CK, et al. Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. J Clin Psychiatry 2001;62:981–984
2. Keck ME, Sillaber I, Ebner K, et al. Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain. Eur J Neurosci 2000;12:3713–3720
3. Keck ME, Welt T, Müller MB, et al. Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. Neuropharmacology 2002;43: 101–109
4. Strafella AP, Paus T, Barrett J, et al. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 2001;21:RC157
5. Jarvik ME, Madsen DC, Olmstead RE, et al. Nicotine blood levels and subjective craving for cigarettes. Pharmacol Biochem Behav 2000;66:553–558
6. Jones RT, Benowitz NL. Therapeutics for nicotine addiction. In: Davis KL, Charney D, Coyle JT, et al, eds. Neuropsychopharmacology: The Fifth Generation of Progress. Philadelphia, Pa: Lippincott Williams & Williams; 2002:1533–1543
7. Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. Eur J Pharmacol 2000;393:295–314
8. Epping-Jordan MP, Watkins SS, Koob GF, et al. Dramatic decreases in brain reward function during nicotine withdrawal. Nature 1998;393: 76–79
9. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 1997;337: 1195–1202
10. Holm KJ, Spencer CM. Bupropion: a review of its use in the management of smoking cessation. Drugs 2000;59:1007–1024
11. Heatherton TF, Kozlowski LT, Frecker RC, et al. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991;86:1119–1127
12. Cousins MS, Stamat HM, de Wit H. Acute doses of d-amphetamine and bupropion increase cigarette smoking. Psychopharmacology (Berl) 2001; 157:243–253
13. King AC, Meyer PJ. Naltrexone alteration of acute smoking response in nicotine-dependent subjects. Pharmacol Biochem Behav 2000;66: 563–572
14. Schuh KJ, Stitzer ML. Desire to smoke during spaced smoking intervals. Psychopharmacology (Berl) 1995;120:289–295
15. Dallery J, Houtsmuller EJ, Pickworth WB, et al. Effects of cigarette nicotine content and smoking pace on subsequent craving and smoking. Psychopharmacology (Berl) 2003;165:172–180
16. Pinheiro JC, Bates DM. Mixed-Effect Models in S- and S-Plus. New York, NY: Springer-Verlag; 2000
17. Benowitz NL. Pharmacokinetic considerations in understanding nicotine dependence. In: CIBA Foundation Symposium 152. The Biology of Nicotine Dependence. Chichester, England: Wiley; 1990: 186–209
18. Ben-Shachar D, Belmaker RH, Grisaru N, et al. Transcranial magnetic stimulation induces alterations in brain monoamines. J Neural Transm 1997;104:191–197
19. Henningfield JE, Schuh LM, Jarvik ME. Pathophysiology of tobacco dependence. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995: 1715–1729
20. Balfour DJ, Ridley DL. The effects of nicotine on neural pathways implicated in depression: a factor in nicotine addiction? Pharmacol Biochem Behav 2000;66:79–85