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ORIGINAL INVESTIGATION

Sung Kil Min · In-Won Moon · Ryeo Won Ko
Ho Sang Shin

Effects of transdermal nicotine on attention and memory in healthy elderly non-smokers

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Abstract *Rationale:* Nicotine has been found to improve cognitive functions in patients with Alzheimer's disease, but little is known about its effects in the healthy non-smoking elderly. *Objectives:* This study aimed to investigate the effects of nicotine on cognitive function in healthy non-smoking or nicotine-na elderly subjects. *Methods:* A transdermal patch containing either 5 mg nicotine or placebo was applied on the back of 63 healthy nicotine-na or non-smoking elderly Koreans. Cognitive functions were evaluated with the Short Blessed Test, Rey-Kim Memory Test, and digit span test of the Korean-WAIS, both before and 5.5 h after nicotine administration. The plasma level of nicotine after testing was measured using gas chromatography. *Results:* The subjects' memory functions in trial 5 of the Rey-Kim Memory Tests improved significantly. Furthermore, the effect on memory slope was significantly correlated with the higher plasma level of nicotine. However, the other tests did not reveal any correlation to a significant degree. *Conclusions:* These results suggest that nicotine of lower plasma level can improve short-term verbal memory functions in non-smoking or nicotine-na healthy elderly people and that some effects are dependent on nicotine plasma levels.

Keywords Nicotine · Elderly person · Attention · Memory · Nicotine plasma level

S.K. Min (✉) · R.W. Ko
Department of Psychiatry, Yonsei University College of Medicine, CPO Box 8044, Seoul, Korea
e-mail: skmin518@yumc.yonsei.ac.kr
Tel.: +82-2-3615475, Fax: +82-2-3130891

I.-W. Moon
Seoul Metropolitan Mental Hospital, Eunpyong-Ku, Seoul, Korea

H.S. Shin
Department of Environmental Education,
Kongju National University, Kongju Chungcheungnam-Do, 314-701, Korea

Introduction

Clinical data suggest that nicotine or nicotinic drugs improve cognitive functions such as attention, memory, and learning in patients with Alzheimer-type dementia (Newhouse et al. 1988; Jones et al. 1992; Wilson et al. 1995; White and Levin 1999). These improvements have also been reported in patients with Parkinson's disease, schizophrenia, and attention deficit hyperactivity disorder (Levin and Rezvani 2000) as well as in both healthy adult smokers (Williams 1980; Mancuso et al. 1999) and non-smokers (Levin et al. 1998). These reported clinical effects have been supported by basic studies on animals (Levin and Simon 1998), on the effects of nicotine on beta amyloid (Salomon et al. 1996) and on the relationship between neuronal nicotine acetylcholine receptors in the brain and complex cognitive functions such as attention and memory as well as neuropsychiatric disorders including Alzheimer's and Parkinson's diseases (Mihailescu and Drucker-Colin 2000). All these studies suggest that nicotine, as a prototype compound for the family of nicotinic compounds, can be an instrument for the investigation of the biology of cognitive function, and that it is one of the possible candidates from which a new nicotine analog can be developed for preventing or treating dementia related with aging and which selectively interact with nicotine receptors without addiction potential (Dursun and Kutcher 1999; Levin and Rezvani 2000).

However, clinical studies on the effects of nicotine on cognitive functions have not produced consistent results. Some other studies have reported that nicotine has little effect on memory or learning functions (Heishman et al. 1993), on attention (Snaedal et al. 1996), or on general cognitive functions of schizophrenic patients (Min et al. 1997). The reasons for these inconsistencies are not known yet. It may be due to differences in subjects or methods of studies, or possibly the effects of nicotine on cognitive functions may vary according to blood level of nicotine.

Participants in studies on nicotine to date have been mainly young college students, adults (smokers and non-

smokers), or old aged patients with degenerative disorders such as Alzheimer's disease. Hence, it has not been confirmed whether nicotine can improve cognitive function in normal non-smoking elderly persons. For nicotine's potential as a drug for preventing dementia to be evaluated, it is necessary to study healthy elderly people in whom dementia may develop in the future.

Smoking or non-smoking is another controversial issue with respect to research methods. If subjects are smokers, it is difficult to differentiate the nicotine effects from reversal of nicotine withdrawal syndrome (Hughes 1991). Among nicotine administration methods such as oral, chewing, smoking, or intravenous, the transdermal nicotine delivery system is considered to be superior because of its pharmacokinetic advantages such as controlled absorption, stable steady-state levels of plasma nicotine after administration, convenience of making placebo, and lack of compounding with the sensory–motor effects of the smoking act (Gorsline et al. 1993; Warburton and Mancuso 1998).

The present study aims to investigate if nicotine can improve cognitive functions such as memory, learning ability, and attention in healthy elderly people and to determine how the improvement is correlated with the blood level of nicotine.

Materials and methods

Participants

This was a randomized double-blind parallel study. The participants were 63 elderly male (n=17) and female (n=46) volunteers who were recruited from a local welfare center in Seoul. The inclusion criteria were: (1) 60–69 years of age, (2) absence of physical and/or psychiatric disorders as determined by medical history and physical and mental examination, (3) a score exceeding 11 in the Korean version of the Short Blessed Test (SBT; Lee et al. 1999) to rule out individuals with cognitive deficit, (4) educational attainment above middle school, and (5) nicotine-na or abstinence for at least the previous year (ex-smoker). Participants were excluded if they had been receiving any centrally acting medications in the 2 weeks prior to entry into the study and if they had a history of alcoholism, drug abuse, or skin problems. After procedures were fully explained, written informed consent was obtained from all participants, and the study was approved by the Ethics Committee of Yonsei University Medical Center, where the study was conducted.

The 63 participants were randomly divided into two groups by simple random numbering, 30 in the placebo group and 33 in the nicotine group. One woman nicotine-na subject in the nicotine group could not finish the study after experiencing nicotine side effects such as nausea, vomiting, and dizziness. Finally, 62 participants (19 males and 45 females) were included in the study. Four males and 31 females were nicotine-na and 17 males and 10 females were ex-smokers. There was no statistically significant difference in mean age, sex ratio, level of education, and marital status between the two groups.

Administration of nicotine

Subjects were given either Nicoderm (ALZA, Kansas, Mo., USA) containing 5 mg nicotine or a placebo which had same form and size as Nicoderm.

In a preliminary study, 7 mg Nicoderm was applied to three participants, two of whom developed side effects of nausea, vomiting, and dizziness. However, in another three participants a lower level of 5 mg Nicoderm did not cause any side effects. Accordingly, the application of 5 mg Nicoderm was chosen. The site of application was the back, since no difference in blood nicotine level has been reported among various sites of application (Gorsline et al. 1992). In addition, the back was reported by participants to be the most convenient site.

Cognitive function tests

Cognitive function tests were composed of the Short Blessed Test (SBT), the Rey-Kim Memory Test, and a digit span test of the Korean Wechsler Adult Intelligence Scale (K-WAIS). Testing was performed by trained clinical psychologists.

Short Blessed Test

The SBT of orientation, concentration, and memory is a shortened 6-item version of the 26-item Information-Memory-Concentration Test which proved to be easily administered and highly predictive of the score on the complete test (Katzman et al. 1983). The Korean version of the SBT (Lee et al. 1999) was used in this study. Participants were asked to answer 6 items, which included three questions on orientation; as well as saying the names of weekdays and seasons backwards, repeating the name and address of a memory phrase, and counting from 20 to 1.

Rey-Kim Memory Test

The Rey-Kim Auditory Memory Test (Kim 1999) is a standardized Korean version of the Rey Auditory Verbal Learning Test, which is known to be a reliable measure in the detection and identification of faulty memory mechanisms. The administration includes five successive presentations of a list of 15 words followed by free recall, a 20-min delayed recall, and a 20-min delayed recognition trial. Delayed recognition was measured with a list of 50 words in which the subject was instructed to circle words from the learning list. Included in the statistical analysis were raw scores for the five acquisition trials, the delayed recall trial, the delayed recognition trial, and three process composites scores which included learning slope, memory retention, and retrieval efficiency.

Digit span

The digit span test, taken from K-WAIS (Yeom et al. 1992), measures working memory, short-term memory, and attention. Both the digit forward and backward subtests were measured.

Procedure

Participants were not allowed to take alcohol in the 24-h period before the experimental session nor to take caffeine (coffee, cola, or tea) in the morning of the experimental session.

Participants completed two experimental sessions before and after the administration of placebo or nicotine. The testing was carried out on a double-blind basis. No information was collected upon participants' awareness of their drug status. Baseline testing was performed at 9.00 a.m., then the transdermal nicotine patch or placebo patch was placed on the back of participants at 9.30 a.m., and they stayed in an area near the laboratory reading newspapers, taking a rest, or doing light walking. Participants were asked not to indulge in strenuous exercise or to bathe while the patch was on the skin. At 1:00 p.m., they had a light meal. Testing was repeated at 3:00 p.m. because nicotine blood level has been reported to rise rapidly within 2–4 h after administration and reach its peak level at 3–6 h (Gorsline 1993). After completing tests, 5 ml blood was

drawn at 3:30 p.m. for measuring the plasma nicotine level. Finally patches were removed.

Assay of nicotine in the plasma

To assess the correlation of the plasma nicotine level with the results of the cognitive function tests, the plasma nicotine level was measured using gas chromatography (Shin et al. 1999).

Five milliliters venous blood from patients was collected in a heparinized syringe. The blood samples were centrifuged, and the plasma was separated and stored at –70°C until analysis.

For each analysis, 2 ml human plasma was used. Diphenylamine solution, 25 µl(10 µg/ml), was added as the internal standard to each sample of plasma in a glass centrifuge tube. Six milliliters diethyl ether and 2 g sodium sulfate were added, and tubes were then stoppered, shaken mechanically for 10 min, and centrifuged for 5 min at 1,500 rpm. The organic layer was transferred to a 15-ml glass centrifuge tube containing 0.5 ml methanol, and evaporated to 0.5 ml residual solvent with a nitrogen stream. The solution was dried with sodium sulfate and injected into a gas chromatograph.

Gas chromatography experiments were performed with a Hewlett-Packard (Avondale, Pa., USA) 5890 series II gas chromatograph with a nitrogen phosphorus detector. HP-5 capillary column (cross-linked 5% phenyl methyl silicon, 25 m × 0.2 mm I.D. × 0.33 µm F.T.) was used for the analysis. The chromatogram of the extract of blood sample extracts was spiked with nicotine (50 ng/ml) and internal standard (125 ng/ml). The retention times of nicotine and internal standard were 5.07 and 6.78 min, respectively. The peaks of nicotine and internal standard were symmetrical and no tailing could be seen. No interfering peak from endogenous substances was observed.

Statistics

A *t*-test was used to assess the effect of nicotine in the nicotine group as compared with the placebo group. Repeated measures general linear model (GLM repeated measure) was used to examine the differences among the cognitive function test scores measured for each subject repeatedly before and after nicotine administration. The cognitive functions test scores were assigned to be the within-subjects factor and the kind of group (nicotine or placebo) as the between-subjects factor. Participants were divided to three groups based on blood level percentile; those who ranked from 0 to 33.3% were assigned to the low level group (<5.3 ng/ml, n=11), from 33.4% to 66.6% to the middle level group (5.3–7.2 ng/ml, n=10), and from 66.7% to 100% to the high levelgroup(>7.2 ng/ml, n=11). Analysis of variance (ANOVA) was used to assess the effect of three different nicotine plasma levels on those cognitive functions test scores in the nicotine subgroups. Pearson's correlation coefficient was computed to measure the linear association between nicotine plasma level and cognitive functions test scores. The statistical significance level was established at 0.05.

Results

Nicotine level

The mean plasma concentration of nicotine 6 h after attachment of the 5 mg nicotine patch was 6.7 ng/ml and its standard deviation was 3.6 ng/ml, with a range from 2.9 to 21.1 ng/ml. No significant difference between men and women (F=1.683, P=0.204) was found in nicotine blood level. Nicotine was not detected in any control samples.

Cognitive function tests

Short Blessed Test

After the nicotine patch administration, the SBT total score declined from 2.72±4.34 to 1.78±3.10 while it de-

Table 1 The effect of the nicotine patch on the cognitive functions

Test name	Group	Before patch Mean ± SD	After patch Mean ± SD	Test and group interaction			
				Wilks's lamda	*df*	*F* value	*P* value
Short Blessed Test	Nicotine	2.72±4.34	2.78±3.10	0.986	1	0.854	0.359
	Placebo	3.77±5.04	3.50±3.03				
Digit span	Nicotine	10.09±3.17	10.00±2.68	0.955	1	0.514	0.476
	Placebo	10.23±3.29	10.97±3.68				
Trial 1	Nicotine	4.16±2.00	9.38±3.10	0.988	1	0.722	0.399
	Placebo	3.90±1.54	8.47±3.03				
Trial 2	Nicotine	7.00±2.09	10.50±2.58	0.994	1	0.370	0.545
	Placebo	6.70±1.56	9.83±2.64				
Trial 3	Nicotine	8.09±2.33	11.47±2.36	0.993	1	0.406	0.526
	Placebo	8.03±2.28	11.03±2.40				
Trial 4	Nicotine	9.44±2.17	11.63±2.24	1.000	1	0.013	0.936
	Placebo	9.07±2.52	11.30±2.18				
Trial 5	Nicotine	10.59±2.20	12.41±2.56	0.915	1	5.604	0.021
	Placebo	10.33±2.14	11.03±2.43				
Delayed recall	Nicotine	8.50±2.76	11.22±2.71	0.993	1	0.419	0.520
	Placebo	7.57±3.37	9.90±3.62				
Delayed recognition	Nicotine	13.19±1.49	14.06±1.05	0.983	1	1.039	0.312
	Placebo	12.33±2.01	13.57±1.56				
Learning slope	Nicotine	6.44±2.08	3.03±2.15	0.993	1	0.411	0.524
	Placebo	6.43±2.06	2.57±2.39				
Memory retention	Nicotine	2.09±1.25	1.19±0.97	0.960	1	2.510	0.118
	Placebo	2.77±1.91	1.13±2.16				
Retrieval efficiency	Nicotine	4.69±2.62	2.84±2.14	0.979	1	1.295	0.260
	Placebo	4.77±2.49	3.67±3.36				

clined from 3.77±5.04 to 3.50±3.03 in the placebo group, a difference that was not statistically significant in the GLM repeated measure method (F=0.854, P=0.359; Table 1). No significant difference was found between men and women in SBT score.

When subjects in the nicotine group were divided into three groups by plasma nicotine level, the mean total score of the SBT showed no significant difference among the three groups (F=0.142, P=0.868). The SBT score in the nicotine group did not significantly correlate with the nicotine plasma level, either (r=0.154, P=0.417)

Rey-Kim Memory Test

There was a significant effect of nicotine on verbal learning over five acquisition trials, as reflected in the score of the learning slope. Improvement in the learning slope showed a significant difference after nicotine patch administration among three groups with different plasma levels [F(1,2)=4.236, P=0.024]. *Post hoc* analysis showed a significant subgroup difference between the high plasma level subgroup (mean=4.36, SD=2.77) and the low blood level subgroup (mean=2.00, SD=1.41). Also the score in the learning slope in the nicotine group was significantly correlated with nicotine plasma level (r=0.445, P=0.014).

Digit span

Nicotine did not exert significant effects on digit span. The mean score of digit span in the nicotine group decreased from 10.09 (SD=3.17) to 10.00 (SD=2.68), while in the placebo group increased from 10.23 (SD=3.29) to 10.97 (SD=3.68) after patch administration. There was no interaction between test and group (F=0.864, P=0.359; Table 1). No significant difference in the score was found between men and women.

Digit span showed no significant difference among the three subgroups with different nicotine plasma levels [F(1,2)=1.809, P=0.182]. Furthermore, the digit span score was not significantly correlated with nicotine plasma level in the nicotine group (r=–0.326, P=0.079).

Discussion

The results of this study suggest that nicotine of a relatively low dose can improve some cognitive functions such as verbal learning in healthy elderly non-smoking or nicotine-na Koreans. These results are in agreement with those of previous studies reporting the improving effects of nicotine on cognitive functions in different ethnic groups.

Measured by the SBT for simple orientation, concentration, and memory, nicotine produced some improvement, but not to a statistically significant degree. Because the SBT measures cognitive impairment for simple and familiar conditions, normal elderly individuals might make so few errors that a low dose of nicotine would not be able to produce significant improvement. In this study, only the digit span test was used for attention, and the results suggest that nicotine did not improve immediate auditory span for digits. This finding concurs with studies which suggest similar insignificant findings (Heishman et al. 1993; Snaedal et al. 1996; Min et al. 1997), but does not with some other studies supporting the positive effects of nicotine (Williams 1980; Jones et al. 1992; Wilson et al. 1995; Mancuso et al. 1999; Levin and Rezvani 2000). These discrepancies may be due to differences in subjects, methods, and cognitive tasks. With a larger sample size and with a higher dose of Nicoderm, more significant results on the effect on attention might be gained.

In verbal learning and rote verbal memory measured with the Rey-Kim Memory Test, recall on trial 5 showed significant improvement after nicotine administration. As recall on trial 1 represents immediate memory span for words, this result suggests that nicotine did not improve the word span itself as much as the digit span. On the contrary, as recall on trial 5 provides a measure of retention for newly learned information, these results suggest that nicotine may facilitate retention or the input of information to storage of a repeated verbal list. In other words, the main effect of nicotine in this study is thought to be improved retention of newly learned information.

However, it is not clear in this study what kind of neurochemical mechanism actually underlies these improvements. The most consistent finding of nicotine effects on human cognition has been reported to be the improvement of vigilance and rapid information processing (Wesnes and Warburton 1983; Warburton et al. 1992). In our study, nicotine seemed to induce some learning or adaptation in which subjects process the information more quickly or screen irrelevant cues more efficiently. As the trials proceeded to trial 5, the nicotine-induced arousal seemed to facilitate immediate recall of the materials while they were being rehearsed. These results suggest that nicotine may have enhancing effects for learning and are compatible with those studies reporting improvement effects of nicotine on short-term memory and learning ability (Warburton et al. 1986, 1992; Levin and Rezvani 2000).

In addition, the improvement in learning slope, which was identified as the difference between recall on trial 5 and trial 1, was significantly correlated with the plasma level of nicotine in this study. Also the improvement was significant in the nicotine subgroup with nicotine plasma level above 7.2 ng/ml compared to the other subgroups with lower nicotine plasma levels. These findings suggest that the effects of nicotine on improving memory depend on the plasma level of nicotine and hence that if the plasma nicotine level were higher, the improvement in other cognitive performances would reach statistical significance.

Several studies indicate that the extent to which the behavior represents acquisition of new learning rather

than old established patterns in part determines its sensitivity to a given dose of nicotine. In reviewing the literature, Levin (1992) suggested that a small dose of nicotine may facilitate acquisition of new learning or memory, but that high doses have no effect or depress it, and that even larger doses might depress established habits. Erickson (1971) suggested that the high dose may cause confusion or excess sensory input via overstimulation. It is known that the dose range that facilitates new learning is a narrow one. It seems probable that the dose range in this study belongs to the low-to-middle portion of the U-shaped dose function. This study, then, suggests that if subjects can tolerate a higher dose, a higher dose of nicotine within a certain level may induce more significant effectiveness.

In animal studies, strain difference in nicotine sensitivity has been found for a variety of neurobehavioral responses (Levin 1992). In this study, the dosage of 5 mg Nicoderm was smaller than the 7-mg doses which were used in other studies with young adults who smoke (Levin et al. 1998). In preliminary work for this study, 7 mg was found to cause side effects in some Korean elderly. Also, this study showed that, in nicotine-na or non-smoking elderly Korean subjects, a smaller dose of 5 mg produced similar effects without causing significant side effects. Further studies are necessary to clarify these differences relating to age, different smoking history, and ethnicity, as well as differences in dosage, task structure, and level of training.

This study was limited by a sample size not big enough to produce significant effects and by a fixed dose of nicotine and limited range of tests preventing the identification of any improvement in other cognitive functions. However, nicotine was shown to improve some cognitive functions depending on plasma level of nicotine and it is suggested that a larger dose of nicotine would significantly improve a wider range of cognitive functions. Further studies with other test methods and various dosages of nicotine are necessary to determine the nicotine effects in many other aspects of cognitive functions.

Though this study did not attempt to reveal the neural mechanism for the nicotine-induced improvement in learning, the results suggest that nicotine, as a prototype compound for the family of nicotinic compounds, is one of the possible candidates from which a new nicotine analog with beneficial effects, fewer adverse side effects, and less addictive potential than nicotine can be developed for preventing or treating dementia related with aging (Dursun and Kutcher 1999; Levin and Rezvani 2000). These new drugs will have a selective interaction with the nicotinic receptor subtype involved in positive nicotine functions but not with the nicotinic receptor subtype that is involved in adverse effects and addictive potential.

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