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Effects of transdermal nicotine on prose memory and attention in smokers and nonsmokers

D.V. Poltavski*, T. Petros[1]

Department of Psychology, University of North Dakota, Grand Forks, ND 58202-8380, USA

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Abstract

Previous research investigating cognitive effects of nicotine has produced mixed findings partly due to the use of abstaining smokers and cigarettes as a delivery system. The present study examined effects of nicotine delivered via a transdermal patch on prose memory and sustained attention in male smokers (n=25) and nonsmokers (n=22), who were randomly assigned to either a placebo or a nicotine condition. All groups were matched on their verbal ability and gross personality characteristics (state/trait anxiety levels, extroversion–introversion, and impulsivity level). In the nicotine condition, smokers were treated with a 21-mg transdermal patch, while nonsmokers received a 7-mg nicotine patch. Six hours following patch application, their performance was assessed on a computerized prose memory task and the Rapid Visual Information Processing task (RVIP) in a counterbalanced order and double-blind fashion. The results demonstrated that smokers in the placebo group recalled a significantly greater number of propositions than their counterparts in the nicotine group. Nonsmokers in the nicotine condition also remembered significantly more of the prose material than smokers in the same condition and showed a trend towards better recall of propositions of medium importance in the nicotine condition in comparison to the nonsmokers in the placebo group. No between-group differences were found on the RVIP task. A significant effect of time was found for systolic blood pressure and heart rate. The results cannot be interpreted using the arousal theory of nicotine effects on attention and are explained on the basis of a dose-dependent nicotinic action possibly recruiting cholinergic cortical projections.

Keywords: Nicotine; Transdermal patch; RVIP; Memory; Attention; Prose; Passages; Nonsmokers; Arousal

1. Introduction

Nicotine is a psychoactive, highly addictive substance with predominantly stimulant effects that increases release of a number of neurotransmitters in the brain, including acetylcholine (ACh), dopamine (DA), serotonin (5-HT), and norepinephrine (NE), by binding to nicotinic cholinergic receptors (nAChRs) [1]. The effects of nicotine depend critically on the dose and speed of administration [1,2]. Its excitatory cholinergic action has been implicated in altered cognitive function in a variety of animal and human studies, including clinical populations (e.g., Refs. 3–7).

Cognitive effects of nicotine in healthy adults have been somewhat obfuscated by the methodological shortcomings that afflicted earlier investigations. In a review of over 100 studies examining effects of nicotine on cognitive performance of normal adults, Heishman et al. [8] noted that a great number of experiments used abstaining smokers. Consequently, the observed improvements could have been produced by withdrawal relief rather than direct cognitive enhancement. Furthermore, the researchers pointed out that daily smokers are never completely nicotine-free, and a variable dose of nicotine administered to smokers in different experiments does not allow to accurately establish

* Corresponding author. School of Medicine and Health Sciences, Center for Health Promotion and Translation Research, 501 N. Columbia Road, P.O. Box 9037, Grand Forks, North Dakota 58202-9037, USA. Tel.: +1 701 777 3077; fax: +1 701 777 2387.

E-mail addresses: dpoltavski@medicine.nodak.edu (D.V. Poltavski), thomas_petros@und.nodak.edu (T. Petros).

[1] Tel.: +1 701 777 3260; fax: +1 701 777 3454.

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the impact of nicotine due to the unknown preexisting plasma nicotine concentration. Another criticism referred to the use of cigarettes as a nicotine delivery system. For instance, it is well known that people differ in their puffing and inhalation strategies and are able to adjust their smoking behavior to partially compensate for actual or perceived changes in the nicotine yield of cigarettes [9,10]. Thus, the use of cigarettes varying in nicotine yield does not guarantee effective dose manipulation. Finally, the use of cigarettes does not allow for the use of an effective placebo control.

Some of the more recent studies have focused on the use of a transdermal nicotine patch as the primary nicotine delivery system (e.g., Refs. [6,11–13]). In these studies, the most consistent finding of nicotine effects on human cognition was improved vigilance (sustained attention) and information processing. Such effects are thought to be primarily mediated by $\alpha 4\beta 2$ cholinergic receptor subtypes [3] mainly in the bilateral parietal and occipital cortices, thalamus, and caudate [14]. Thus, cholinergic nicotinic action is thought to influence more of the visual attention/arousal aspects of the task rather than working memory/target detection functions associated with the frontal cortical regions [14]. Additional positive effects of nicotine on inhibition and sustained attention might be derived from its enhancing dopaminergic action in the striatal–frontal and mesocortical dopaminergic systems [15]. For example, in a series of experiments, Shoaib and Bizarro [16] showed that blockade of D1 dopaminergic receptors in rats chronically treated with nicotine resulted in significant decrements in performance on a task measuring sustained attention, which were similar to the deficits observed on the same task in nicotine-deprived rats.

Warburton and Mancuso [11] examined the effects of nicotine delivered via a transdermal patch (21 mg/day) on the performance of smokers on a variety of cognitive tasks including those of attention and memory. It was previously established that 6 h after the activation of the patch, a 21-mg dose produces average levels of nicotine similar to trough levels which are found in a smoker on an average smoking day, i.e., about half of the peak levels achieved at the end of each cigarette [15]. Stable isotope analysis of transdermal nicotine absorption also showed that the maximum rate of absorption occurs between 6 and 12 h after the activation of the patch. Unlike cigarette smoking, which results in rapid delivery of nicotine to the bloodstream, transdermal nicotine systems result in a different blood concentration—time profile, without the peaks and troughs characteristic of cigarette smoking [17].

In their experiment, Warburton and Mancuso [11] used four types of tests: attention testing (Rapid Visual Information Processing, RVIP), memory tests (verbal and nonverbal), problem solving (Semantic Verification Test), and mood assessment. The results indicated improved performance of smokers in the nicotine condition on the RVIP test (faster reaction times, greater accuracy, and fewer number of errors of commission), improved immediate and delayed recall of word lists, and improved mood characterized by the feelings of relaxation and calmness. The nicotine patch, however, was not found to affect either the number of correct responses or reaction time on the Semantic Verification Test or to significantly influence performance on nonverbal memory tests [11].

In a subsequent study, Mancuso and Warburton [12] used a 21-mg nicotine patch to assess performance of 24 heavy smokers (over 15 cigarettes/day) on a battery of cognitive measures (Random Letter generation test, the Flexibility of Attention test and the Stroop test) 3 and 6 h after the application of the patch. The researchers found no differences in performance between the nicotine and the placebo conditions on any of the tests after 3 h of patch application. However, after 6 h, nicotine-treated participants completed the Stroop task significantly faster both in the control condition and in the interference condition.

At the same time, a plateau in nicotine blood concentration levels might not be necessary to detect significant changes in performance on measures found to be particularly sensitive to nicotine, such as RVIP [18]. In another study employing a within-subjects placebo-controlled design, Mancuso et al. [6] tested 15 young (18–25 years old) male smokers (over 15 cigarettes/day) on the RVIP task 1.5, 3, and 6 h following a 21-mg nicotine patch application. Although at all three points in time participants demonstrated a significantly greater number of hits in the nicotine condition than in the placebo condition, there were no significant differences between any of the time periods. No significant differences between the placebo and nicotine conditions were found for reaction time. Similarly, reaction times did not significantly differ for any of the application intervals. The authors suggested that the observed counterintuitive dissociation between the probable pharmacokinetics of nicotine and the time-course of its attentional effects might be due to acute tolerance to nicotine-induced cognitive changes, particularly on the RVIP task. It can also be argued that a small dose of nicotine (obtained as early as 1.5 h after patch application) is sufficient to produce a significant improvement in performance on a task particularly sensitive to nicotine.

While ameliorating effects of nicotine in the very least on measures of sustained attention (e.g., RVIP, CPT) have been somewhat well-established, its effects on verbal recall (both immediate and delayed) have been less conclusive.

Earlier studies involving abstinent and nonabstinent smokers and using cigarettes for nicotine delivery found improved immediate recall of prose passages [19] and semantically related word lists (e.g., Refs. [20,21]), while recall of unrelated word lists depended on the length of the lists used, showing significant improvement following nicotine administration in studies employing longer lists (e.g., Ref. [22]). Initially, the data were consistent with the suggestion that nicotine might be improving memory by improving attention at the encoding stage [21]. However,