Pharmacology Biochemistry & Behavior, Vol. 39, pp. 265–268. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

The Effects of Smoking-Related Sensory Cues on Psychological Stress

EDWARD D. LEVIN,*†[1] JED E. ROSE,*† FREDERIQUE BEHM*† AND NICHOLAS H. CASKEY‡

**Nicotine Research Laboratory, VA Medical Center, Durham, NC*
†Department of Psychiatry, Duke University, Durham, NC
‡Psychopharmacology Research Laboratory, VA Medical Center, Los Angeles, CA

Received 26 November 1990

LEVIN, E. D., J. E. ROSE, F. BEHM AND N. H. CASKEY. *The effects of smoking-related sensory cues on psychological stress*. PHARMACOL BIOCHEM BEHAV **39**(2) 265–268, 1991.—Previous studies have shown that the sensory cues of cigarette smoking are important for smoking satisfaction and craving reduction. Sensory cues in the absence of pharmacological doses of nicotine have been found to be moderately satisfying and to reduce craving. The current study was conducted to determine if administration of the sensory cues of cigarette smoking with minimal nicotine would also provide relief from mild anxiety associated with anticipation of a difficult anagram test. This test has previously been shown to be sensitive to the anxiety relieving effects of cigarette smoking. Compared to the placebo control condition, the sensory condition caused a significant alleviation of the stress as measured by components of the Spielberger scale for anxiety. The addition of cigarette smoke containing 0.5 mg of nicotine to the sensory cues caused a slight though nonsignificant enhancement of the stress alleviation. These results demonstrate that sensory cues of smoking can provide similar effects as nicotine containing cigarettes with regard to stress alleviation. Previous studies had shown that sensory cues are important for the consumptive aspects of smoking (i.e., smoking satisfaction and craving reduction). The current study shows that sensory cues are important for other effects of smoking as well.

Smoking Stress Anagrams Sensory Aerosol

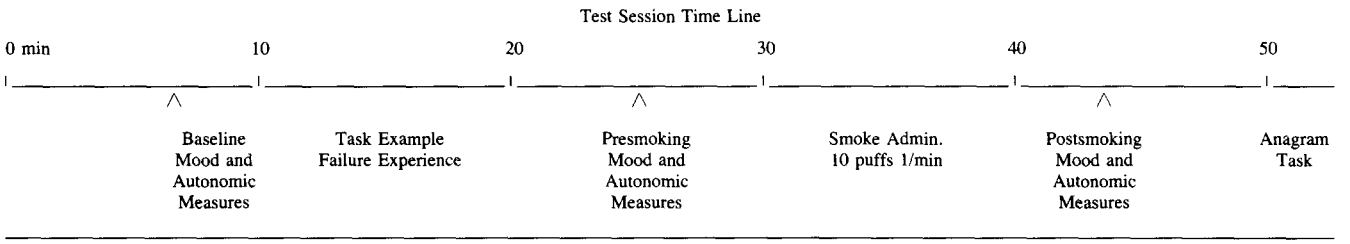
RECENT findings from our laboratory and others suggest that the sensory aspects of nicotine and other components of cigarette smoke have prominent behavioral effects (2, 18, 20, 23). Nicotine itself is an irritant (5,25) and is probably one of the principal constituents responsible for the "throat scratch" sensation that smokers report enjoying during the act of inhaling cigarette smoke. In addition, the perception of the flavor of smoke is an important component of the satisfaction reported by smokers (17). We have recently developed a method for refining cigarette smoke to keep many of the sensory aspects of smoking while eliminating most of the nicotine, tar and carbon monoxide delivery (1,20). Subjects report an experience very much like smoking a real cigarette despite the 5–10-fold reduction in nicotine delivery and 10–20-fold reduction in tar delivery and no delivery of carbon monoxide. These important peripheral cues may be either conditioned or unconditioned stimuli producing many of the immediate effects of smoking including smoking satisfaction and reduction of craving for cigarettes (1,20). This effect can also be seen with administration of citric acid aerosol which contains no nicotine (11,21). Conversely, blocking the sensory stimulation of the throat associated with cigarette smoking significantly reduces smoking satisfaction (18, 23, 24). In addition to satisfaction and craving reduction, the sensory cues of smoking may also be important in producing other effects of smoking not related to consumption.

Smokers often report that smoking a cigarette alleviates stress (4,13) and anxiety-provoking situations increase the consumption of cigarettes (19). These reports seem paradoxical in light of the findings that smoking increase sympathetic arousal associated with stress (14). As an explanation of this paradox, Gilbert (7) proposed that nicotine may interfere with the perception of sympathetic arousal. However, smoking was not found by Lombardo and Epstein (12) to reduce perception of changes in pulse rate. That is not to say that smoking or nicotine administration does not have any effects on interoception of stress-related events. In an earlier study, Epstein et al. (6) found that cigarette smoking reduced perceptual sensitivity to forearm flexor electromyographic changes. Smoking nicotine-containing cigarettes has been found to reduce the anxiety in anticipation of having to solve a difficult anagram (9, 15, 16). Stress-reducing effects of smoking would be a prime mechanism to consider in accounting for the influence of stress on cigarette smoking and relapse after smoking cessation. Nicotine has received much attention as a possible stress-reducing agent in cigarette smoke, and most theories have assumed that the direct actions of nicotine on the central nervous system are critical in mediating any effects on the perception of stress. However, the conditioned sensory cues of smoking may become important for many of the effects of smoking (22). Our previous research has demonstrated that the sensory aspects of smoking are important with regard to smoking satisfaction and craving reduction. Whether the sensory aspects of smoking are important for effects of smoking not related

[1]Requests for reprints should be addressed to Dr. Edward D. Levin, Nicotine Research Laboratory-151S, VA Medical Center, 508 Fulton St., Durham, NC 27705.

TABLE 1

TIME LINE OF EVENTS IN THE EXPERIMENTAL SESSION



to evaluation of and craving for smoke consumption remains unknown. The current study was designed to evaluate the importance of sensory cues for one of these nonconsumptive effects: stress reduction. The hypothesis was that administration of the regenerated smoke would be effective in reducing stress like cigarette smoke does even though it contained very little nicotine.

METHOD

Subjects

Participants in the study were 59 healthy smokers (42 male and 17 female) aged 18–50 years who smoked an average of at least 20 cigarettes (0.7–1.2 mg/cigarette by FTC analysis) per day for the past two years. The subjects underwent overnight smoking deprivation prior to the study. The control group had 14 subjects and each of the other three treatment groups had 15 subjects.

Experimental Design and Procedure

In a between-subjects design, the effects of smoking a cigarette and/or a cigarette substitute were measured on the subjective reports of mood and anxiety and cardiovascular responses of subjects during a mildly stressful period. A time line of the study session is shown in Table 1. There were four treatment groups. The placebo group puffed on nebulized water. The condensate group puffed on a nebulized aerosol of cigarette smoke condensate suspended in water. The condensate + cigarette group puffed on an equal volume mixture of the nebulized condensate aerosol and fresh smoke from a cigarette (Marlboro). The cigarette group smoked only the fresh smoke from a Marlboro cigarette.

The stress used was anticipation of failure in an anagram test. Anticipation of failure in a test of difficult anagrams has previously been shown to elicit a type of anxiety which is reduced by smoking cigarettes (9,16). In the current study each subject was first given a very difficult sample anagram test during an orientation portion of the test session. They were told that this was a practice test and that another one would be given later in the session for which they would receive 25 cents for each correct answer. This pretest was made up of the 16 of the most difficult anagrams of a list of 378 assessed by Tresselt and Mayzner (28). They calculated the median time to solve these anagrams in a group of 20 normal subjects. The average median time to solve each of these 16 difficult anagrams was 231 seconds with a maximum allowed time of 240 seconds. Ten of the anagrams on the list were not solved by any of the subjects in the previous study. In the present study, the subjects were given 5 minutes (300 seconds) to finish all 16 of the difficult anagrams. These anagrams have been shown to be sensitive to the stress-alleviating effects of smoking (3). After finishing the anagram test, the subjects answered the POMS test for mood assessment and the Spielberger test for anxiety assessment (27). They also had their blood pressure and pulse rate measured. Then they were given one of the four smoking conditions: placebo, regenerated cigarette smoke aerosol, regenerated smoke aerosol mixed with fresh cigarette smoke, and fresh cigarette smoke alone. The questionnaires and cardiovascular measurements were again taken after smoking. Finally, the subject was given another anagram test for which each correct answer was rewarded with a bonus payment of 25 cents. The second anagram test consisted of 16 easier anagrams which were solved in an average median time of 62 seconds. As with the first test the subjects were given five minutes to solve as many as they could.

Smoke Delivery

The method of sensory cue delivery employed in the current study used refined smoked condensate similar to what we had originally developed (20). In the current experiment instead of generating the aerosol by heat, an aerosol was made by the use of an ultrasonic nebulizer (1). The solution in the nebulizer was 50 mg of refined cigarette smoke condensate in 4 ml of distilled water plus 0.8 ml ethanol. With each puff 3 mg of the solution was delivered. Thus only 0.03 mg of condensate was delivered with each puff. Puff volume (35 cc) was controlled by using an apparatus and procedure developed by Levin et al. (10).

Data Analysis

Because the hypothesis concerned the effects of smoking on stress in anticipation of failure only those subjects who failed the pretest (less than 25% correct) were included in the analysis of smoking effects. The dependent variables consisted of an assessment of subjective mood (the POMS Test and the Spielberger anxiety scale, as well as heart rate and blood pressure). Heart rate and systolic and diastolic blood pressure were measured by an Auto-inflation Digital Sphygmomanometer. Group differences were assessed by analysis of variance. An analysis was conducted to compare the effects of the different levels of nicotine and sensory cue presentation in the placebo, regenerated smoke, regenerated smoke + cigarette smoke and normal strength cigarette smoke conditions.

RESULTS

The subjects in the group which only smoked a cigarette had significantly higher stress and lower mood scores on the baseline Spielberger and POMS tests before any group-related treatments were made. Because of these anomalous baseline scores,

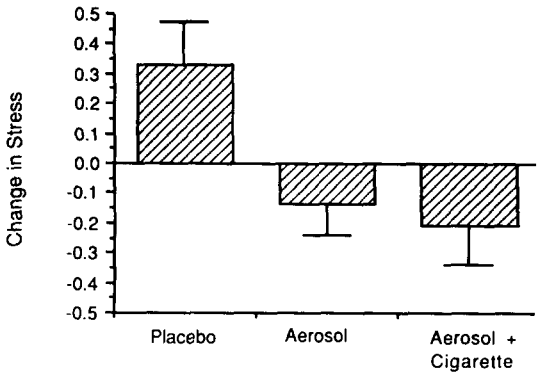


FIG. 1. Spielberger: change in stress. Effect of smoking condition on the cluster of the Spielberger items sensitive to the anxiety-inducing properties of the difficult anagram test.

this group was not considered in subsequent data analysis.

As expected, most of the subjects encountered a failure experience when they took the difficult anagram test. Most subjects had fewer than 25% items correct on this test (10 of 14 subjects in the control group, 11 of 15 in the sensory group and 12 of 15 in the sensory + cigarette group). The anxiety-inducing effect of failing the pretest was assessed prior to the availability of the aerosol mixtures.

Compared to baseline scores, several of the items of the Spielberger anxiety scale were sensitive to the anxiety provoked by failing the test of difficult anagrams. The overall Spielberger scores were not significantly affected by the pretest. The sensitive items of the Spielberger test were: ease ($p<0.06$), tense ($p<0.06$), upset ($p<0.08$) and nervous ($p<0.05$). Curiously, two items detected significant effects in the opposite direction as expected. The subjects reported feeling significantly more joy ($p<0.025$) and significantly less worrying about misfortune ($p<0.01$). The mean of the four items of the Spielberger test which were sensitive to the anxiety-inducing effects of the difficult anagram test (ease, upset, tense and nervous) were then used to assess the effect of the subsequent smoking treatments. The ease question was scored oppositely from the other three since higher scores on this item indicated less rather than greater stress.

There was a significant effect of smoking condition in attenuating the stress induction caused by the difficult anagram test, $F(2,29)=5.01$, $p<0.025$. Comparisons of the effects of the individual treatments revealed that the regenerated smoke aerosol caused a significant attenuation of the stress compared with placebo ($p<0.025$). The same was true for the regenerated smoke aerosol + cigarette condition ($p<0.01$). The regenerated smoke condition did not cause a differential effect relative to the regenerated smoke + cigarette condition. The composite stress scores went up 0.33 ± 0.14 in the placebo group, while they came down -0.14 ± 0.10 in the regenerated smoke group and -0.21 ± 0.13 in the regenerated smoke + cigarette group (Fig. 1). The smoking-induced change in scores for individual items is shown in Table 2. With each of the individual items the regenerated aerosol caused the same lessening of anxiety relative to placebo as the composite score. The differences for the individual items were not significant as the cluster of items was except for the tense item for which the aerosol group showed a marginally significant, $F(1,30)=4.06$, $p<0.06$, greater reduction than the placebo group.

The POMS test was relatively insensitive to the effect of failing the difficult anagram test. Only the confusion cluster on the POMS test yielded a significant effect of failing the difficult anagram test ($p<0.05$). This cluster did not yield a significant effect of smoking condition.

The difficult anagram pretest did not significantly alter pulse rate. The average pulse rate prior to the pretest was 78.1 ± 2.4 (mean $\pm$ standard error of the mean) while the average pulse rate after the pretest was 77.3 ± 2.2. There was a significant, $F(1,29)=4.71$, $p<0.05$, drop in systolic blood pressure from before the pretest (124.6 ± 2.8) to after the pretest (120.1 ± 3.0). No effect of the pretest was seen in terms of diastolic blood pressure. No significant effects on pulse rate and blood pressure were seen with the smoking manipulations. However, there was a trend towards an increased pulse rate in smoking the aerosol + cigarette condition (pre $=76.3 \pm 3.3$, post $=79.6 \pm 3.4$), while there was no hint of increases in pulse rate in the placebo (pre $=81.4 \pm 6.2$, post $=79.3 \pm 5.2$) and aerosol (pre $=77.1 \pm 3.1$, post $=77.1 \pm 4.2$) groups.

DISCUSSION

These results indicate that some of the stress-alleviating properties of cigarette smoke can be evoked by presentation of the sensory cues of smoking without pharmacological doses of nicotine. This provides support for the idea that conditioned cues of smoking are important in determining the psychological effects of smoking (22). However, there is also evidence for direct unconditioned pharmacological effects of nicotinic stimulation in the respiratory tract resulting in muscle relaxation (8). We have previously found that the sensory cues of smoking were important for providing smoking satisfaction and for reducing craving for cigarettes (1, 20, 23). The current results that sensory cues are also important for stress alleviation, provides the first evidence that sensory cues of smoking are important for the effects of smoking that are not related to the act of smoking itself. Perhaps sensory cues of smoking are conditioned to the pharmacological effects of the drug with which it is normally associated.

TABLE 2

EFFECT OF SMOKING CONDITION ON THE INDIVIDUAL ITEMS OF THE SPIELBERGER TEST SENSITIVE TO THE ANXIETY INDUCING PROPERTIES OF THE DIFFICULT ANAGRAM TEST

Group	Ease	Tense	Upset	Nervous
Placebo	−0.50 ± 0.34	0.40 ± 0.22	0.00 ± 0.00	0.22 ± 0.15
Aerosol	0.00 ± 0.19	−0.27 ± 0.14*	−0.18 ± 0.12	−0.09 ± 0.25
Aerosol + Cigarette	0.50 ± 0.36†	−0.08 ± 0.29	−0.08 ± 0.08	−0.17 ± 0.17

*$p<0.06$ vs. placebo, †$p<0.05$ vs. placebo.

In the current study, the addition of nicotine to the presentation of sensory cues (regenerated smoke + cigarette condition) did not cause significantly greater stress reduction than the regenerated smoke alone. It may be possible that there is an additional effect with nicotine but that there was insufficient statistical power of our experiment to detect such an effect. However, if there is an additional effect of nicotine it appears likely that it is small compared to the effect of sensory stimulation.

In the current study, the effects of the regenerated smoke aerosol were tested in smokers deprived of cigarettes since the previous evening. Deprived subjects were studied to further assess the potential of this aerosol for use as an aid in smoking cessation. It remains an open question whether this regenerated smoke aerosol would decrease stress response in nondeprived smokers. It seems likely that it would be less difficult for this low nicotine regenerated aerosol to attenuate stress response in smokers not undergoing nicotine withdrawal. However, smoking deprivation itself elevates stress response which may make it easier to detect attenuated stress response in a deprived group of smokers.

The reduction in anxiety caused by the sensory cues suggests that sensory cues could be used in smoking cessation programs not only to address problems with increased craving for cigarettes, but also to address other unpleasant withdrawal effects not related to the consummatory act of smoking. Deprivation of cigarettes has been found to significantly increase anxiety (26). This may be a contributing factor in relapse. Conditioned sensory cues of smoking may be particularly effective in alleviating withdrawal effects such as increase in negative affect. Preliminary data from clinical studies in our laboratory indicate that this may indeed be the case.

Sensory cues associated with the delivery of nicotine can easily become conditioned stimuli predicting physiological and psychological effects of nicotine. Considering that cigarette smoking pairs a highly characteristic set of cues in close temporal relation to a pharmacological effect thousands of times a year in a moderate smoker, one can easily see how cigarette smoking represents an ideal forum for the development of conditioned reinforcing stimuli. When assessing the pharmacological effects of nicotine delivered by cigarette smoking it is important to remember the cues accompanying the nicotine that is delivered.

ACKNOWLEDGEMENTS

This research was supported by grants from the MacArthur Foundation and NIDA (Grant DA 02665) awarded to J.E.R., and by the Medical Research Service of the Department of Veterans Affairs.

REFERENCES

1. Behm, F. M.; Levin, E. D.; Lee, Y. K.; Rose, J. E. Low-nicotine regenerated smoke aerosol reduces desire for cigarettes. J. Subst. Abuse 2:237–247; 1990.
2. Cain, W. S. Sensory attributes to cigarette smoking. In: Gori, G. B.; Bock, F. B., eds. Banbury Report 3: A safe cigarette? New York: Cold Spring Harbor Laboratory; 1980:239–249.
3. Caskey, N. H.; Jarvik, M. E. Smoking-induced anxiety reduction during anagram stress exposure. Paper presented at the American Psychological Society Convention, Dallas, TX, June 9, 1990.
4. Coan, R. W. Personality variables associated with cigarette smoking. J. Pers. Soc. Psychol. 26:86–104; 1973.
5. Domino, E. F. Neuropsychopharmacology of nicotine and tobacco smoking. In: Dunn, W. L., ed. Smoking behavior: Motives and incentives. Washington, DC: Winston; 1973:5–31.
6. Epstein, L. H.; Dickson, B. E.; McKenzie, S.; Russell, P. O. The effect of smoking on perception of muscle tension. Psychopharmacology (Berlin) 83:107–113; 1984.
7. Gilbert, D. G. Paradoxical tranquilizing and emotion-reducing effects of nicotine. Psychol. Bull. 86:643–661; 1979.
8. Ginzel, K. H.; Eldred, E. Reflex depression of somatic motor activity from heart, lungs and carotid sinus. In: Paintal, A. S.; Gill-Kumar, P., eds. Krogh centenary symposium on respiratory adaptations, capillary exchange and reflex mechanisms. Delhi: Vallabhbhai Patel Chest Institute, University of Delhi; 1977:358–395.
9. Jarvik, M. E.; Caskey, N. H.; Rose, J. E.; Herskovic, J.; Sadeghpour, M. Anxiolytic effects of smoking associated with four stressors. Addict. Behav. 14:379–386; 1989.
10. Levin, E. D.; Rose, J. E.; Behm, F. Controlling puff volume without disrupting smoking topography. Behav. Res. Methods Instr. Comp. 21:383–386; 1989.
11. Levin, E. D.; Rose, J. E.; Behm, F. Development of a citric acid aerosol as a smoking cessation aid. Drug Alcohol Depend. 25:273–279; 1990.
12. Lombardo, T. W.; Epstein, L. The nicotine paradox: Effect of smoking on autonomic discrimination. Addict. Behav. 11:341–344; 1986.
13. McArthur, C.; Waldron, E.; Dickenson, J. The psychology of smoking. J. Abnorm. Psychol. 56:267–275; 1958.
14. Nesbitt, P. D. Smoking, physiological arousal and emotional response. J. Pers. Soc. Psychol. 25:137–144; 1973.
15. Pomerleau, O. F. Nicotine as a psychoactive drug: Anxiety and pain reduction. Psychopharmacol. Bull. 22:865–869; 1986.
16. Pomerleau, O. F.; Turk, D. C.; Fertig, J. B. The effects of cigarette smoking on pain and anxiety. Addict. Behav. 9:265–271; 1984.
17. Reasor, B. A.; Reynolds, M. L.; Ferris, R. P. Sensory assessment of tobacco smoke. Rec. Adv. Tobacco Sci. 14:3–48; 1988.
18. Rose, J. E. The role of upper airway stimulation in smoking: In: Pomerleau, O. F.; Pomerleau, C. S., eds. Nicotine replacement in the treatment of smoking: A critical evaluation. New York: Alan Liss, Inc.; 1988:95–106.
19. Rose, J. E.; Ananda, S.; Jarvik, M. E. Cigarette smoking during anxiety-provoking and monotonous tasks. Addict. Behav. 8:353–359; 1983.
20. Rose, J. E.; Behm, F. M. Refined cigarette smoke as a means to reduce nicotine intake. Pharmacol. Biochem. Behav. 28:305–310; 1987.
21. Rose, J. E.; Hickman, C. Citric acid aerosol as a potential smoking cessation aid. Chest 92:1005–1008; 1988.
22. Rose, J. E.; Levin, E. D. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. Br. J. Addic., in press; 1991.
23. Rose, J. E.; Tashkin, D. P.; Ertle, A.; Zinser, M. D.; Lafer, R. Sensory blockade of smoking satisfaction. Pharmacol. Biochem. Behav. 23:289–293; 1985.
24. Rose, J. E.; Zinser, M. D.; Tashkin, D. P.; Newcomb, R.; Ertle, A. Subjective response to cigarette smoking following airway anesthetization. Addict. Behav. 9:211–215; 1984.
25. Russell, M. A. H. Conceptual framework for nicotine substitution. In: Okene, J. K., ed. The pharmacologic treatment of tobacco dependence: Proceedings of the World Congress, November 4–5, 1985. Institute for the Study of Smoking Behavior and Policy; 1986:90–107.
26. Silverstein, B. Cigarette smoking, nicotine addiction, and relaxation. J. Pers. Soc. Psychol. 42:946–950; 1982.
27. Spielberger, C.; Gorsuch, R.; Lushene, N. Manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologists Press; 1970.
28. Tresselt, M. E.; Mayzner, M. S. Normative solution times for a sample of 134 solution words and 378 associated anagrams. Psychonom. Monogr. Supp. 1(15):293–298; 1966.