Pharmacology Biochemistry and Behavior, Vol. 44, pp. 891-900, 1993
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0091-3057/93 $6.00 + .00
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Role of Nicotine Dose and Sensory Cues in the Regulation of Smoke Intake

JED E. ROSE,[1] FREDERIQUE M. BEHM AND EDWARD D. LEVIN

Nicotine Research laboratory, VA Medical Center, 508 Fulton Street, Durham, NC 27705
Department of Psychiatry, Duke University, Durham, NC 27706

Received 30 April 1992

ROSE, J. E., F. M. BEHM AND E. D. LEVIN. *Role of nicotine dose and sensory cues in the regulation of smoke intake.* PHARMACOL BIOCHEM BEHAV 44(4) 891-900, 1993.—We investigated the role of nicotine dose and sensory cues in the regulation of ad lib smoke intake. The smoking behavior of 12 adult male smokers was assessed in three conditions, presenting either high-nicotine cigarette smoke (*high* nicotine, *high* sensory), diluted cigarette smoke (*low* nicotine, *low* sensory), or an aerosol containing cigarette smoke constituents suspended in solution, which was *low* in nicotine, yet *high* in sensory impact. Subjects showed marked compensatory increases in smoking with the dilute smoke condition, whereas they puffed and inhaled the aerosol to a similar extent as the high-nicotine cigarette. Thus, subjects regulated their smoking behavior to equate sensory intensity rather than nicotine intake. Moreover, the aerosol and high-nicotine cigarette conditions lowered craving to a greater degree than the dilute smoke condition. Other mood indices, such as arousal and negative affect, were more effectively relieved by the high-nicotine dose condition. These results highlight the importance of sensory cues in the regulation of smoke intake and modulation of craving and suggest the clinical application of techniques for providing relief of cigarette craving during smoking cessation.

Cigarette smoking Nicotine Aerosol Sensory Reinforcement Mood

CIGARETTE smokers regulate their intake of nicotine within upper and lower limits to avoid nicotine toxicity from oversmoking and nicotine withdrawal symptoms from undersmoking. They take larger, more frequent puffs and inhale more deeply from low-nicotine cigarettes and take fewer, smaller puffs and inhale less deeply from high-nicotine cigarettes (20). While this "titration" of nicotine intake is far less precise than often supposed (1,11), there is nonetheless some ability on the part of most smokers to compensate for changes in cigarette nicotine delivery. However, it is not known what specific mechanisms account for self-regulation of smoke intake. The effects of nicotine in the CNS are widely believed to account for control of nicotine intake. That is, when the brain has too little nicotinic stimulation smoking is increased and when it receives excessive stimulation smoking is decreased. An alternative, and not necessarily incompatible, hypothesis is that the immediate respiratory tract sensory cues provided by inhalation of each puff of smoke are used to meter nicotine intake (16). Because nicotine is a potent irritant, the perceived strength of smoke in the respiratory airways is a good predictor of nicotine dose (9). Nicotine delivery and sensory impact are highly correlated for most commercial brands of cigarette, and, in particular, low-tar and -nicotine cigarettes that dilute smoke via ventilation holes have weak sensory properties compared to high-nicotine cigarettes. Of special importance may be the fact that these brands produce less intense respiratory tract sensations than more popular brands of cigarette.

To dissociate nicotine dose, and hence direct CNS effects, from sensory impact, we used an aerosol that is low in nicotine but high in sensory impact (2,17). In our procedure, cigarette smoke constituents are collected, suspended in solution, and reaerosolized. Using an ultrasonic nebulizer, the particle size of the resulting aerosol is larger than cigarette smoke so that proportionally more particles deposit in the upper airways, where most smoking-related sensations are perceived (5, 13,16,19). Thus, with only a small amount of tar and nicotine the impression of a strong cigarette is created. Previously, we reported that inhalations of a low-nicotine regenerated smoke aerosol reduced the desire for cigarettes as much as a popular commercial brand of cigarette delivering 20 times more nicotine, and the aerosol was perceived as having a strength comparable to that high-nicotine cigarette (2). The present study extends these results by showing that compensatory increases in smoking behavior typical of low-nicotine cigarettes do not occur with a low-nicotine aerosol that provides sensations like those from a high-nicotine cigarette.

Subjective ratings of liking and satisfaction were collected, and a direct test of preference between the regenerated smoke aerosol and the low-nicotine cigarette condition was con-

[1] To whom requests for reprints should be addressed.

ducted, to assess whether any aversive effects of the aerosol may have limited smoking behavior in that condition.

METHOD

Subjects

Twelve male smokers were recruited through newspaper advertisements; their mean age was 33 years (SD = 8.4) and they smoked an average of 30 cigarettes/day (SD = 8.9), having a nicotine delivery (by FTC analysis) of 0.9 mg (SD = 0.12). Subjects had smoked an average of 14.5 years (SD = 7.8)

Apparatus

Smoke presentations. Three types of smoke were presented to subjects. These were designed to dissociate nicotine delivery from the intensity of smoking-related respiratory tract sensations. These conditions were as follows: a) high-nicotine cigarette (*high* nicotine, *high* sensory). A Winston 85-mm cigarette was smoked through a special holder that trapped one eighth of the mainstream smoke particles while leaving unaffected the other seven eighths of smoke particles and the entire delivery of CO and other gaseous smoke constituents (see Fig. 1); b) low-nicotine cigarette (*low* nicotine, *low* sensory). In this condition, a Winston cigarette was smoked through a holder that trapped approximately seven eighths of the mainstream particulate matter (see Fig. 2). Thus, the tar and nicotine delivery for a constant volume puff was reduced to one eighth of the usual but the delivery of CO and other gases was held constant; c) low-nicotine regenerated smoke aerosol (*low* nicotine, *high* sensory). For this condition, cigarette smoke particulate matter was collected by impaction in a glass tube (17) and suspended in water (2% w/w), with sorbitan trioleate (1.5%) as an emulsifier. An ultrasonic nebulizer was used to generate an aerosol from this solution that subjects could inhale. A typical 40-cc puff of aerosol delivered approximately 5 mg solution, containing 0.1 mg tar and 0.006 mg nicotine, roughly 5% of the delivery of the full-strength Winston cigarette. A lit Winston cigarette was connected in series with a Cambridge filter and the nebulizer so that, with each puff, only the gaseous smoke constituents from the Winston were drawn through the nebulizer, where they picked up aerosol droplets and passed into the subject's mouth (see Fig. 3). Therefore, the CO delivery for a constant-volume puff was the same as in the other two conditions but the nicotine delivery was low. This allowed us to use expired air CO and number of cigarettes smoked as indices of smoking intensity for all conditions, which would not otherwise be possible for the regenerated smoke aerosol. As mentioned above, the sensory impact of the aerosol was high, relative to the comparably sized puffs from a low-nicotine cigarette, because the particle size of the regenerated smoke aerosol was greater than that of cigarette smoke (2.5 vs. 0.5 μm mass median diameter).

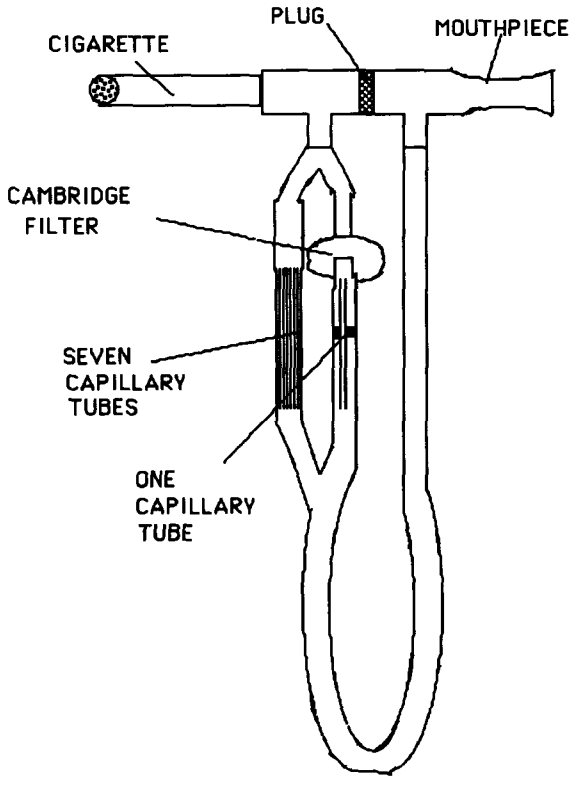

FIG. 1. Apparatus for presentation of high-nicotine, high-sensory smoke. A high-nicotine cigarette was smoked through a device that trapped one eighth of the mainstream smoke particles, while leaving unaffected the other seven eighths of smoke particles and the entire delivery of CO and other gaseous smoke constituents.

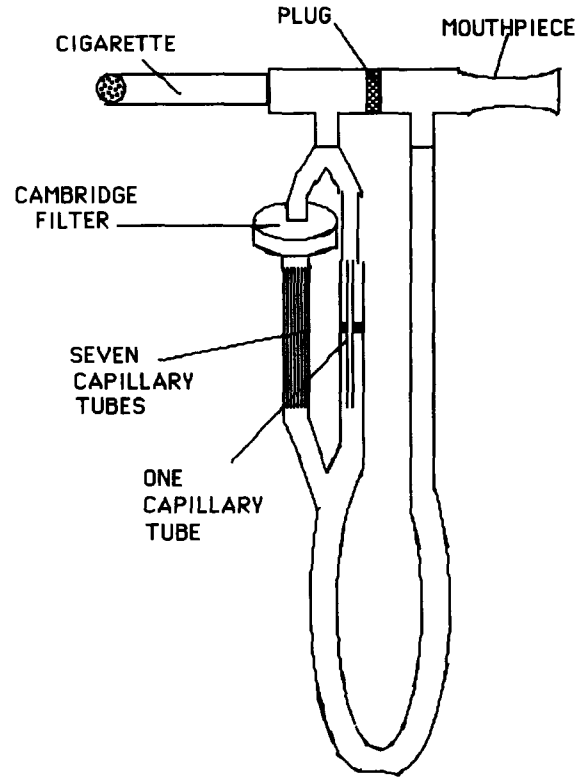

FIG. 2. Apparatus for presentation of the low-nicotine, low-sensory condition. A cigarette was smoked through a device that trapped approximately seven eighths of the mainstream particulate matter, while leaving unaffected the delivery of CO and other gases.

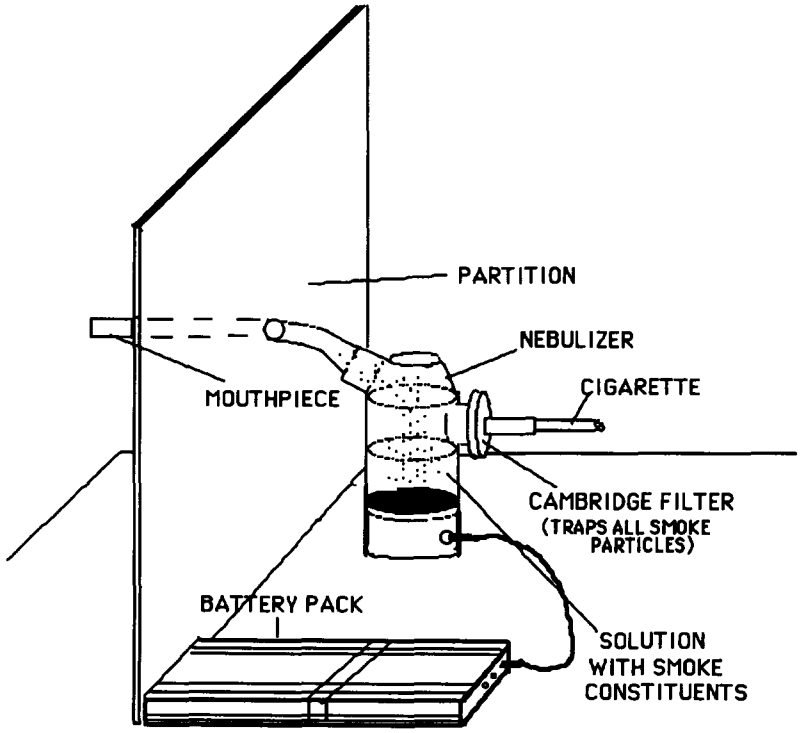

FIG. 3. Apparatus for presentation of the low-nicotine, high-sensory condition (regenerated smoke aerosol). An ultrasonic nebulizer generated an aerosol from a solution of smoke particulates. A lit cigarette was connected to a Cambridge filter and the nebulizer so that only the gaseous smoke constituents were drawn through the nebulizer and conveyed the aerosol into the subject's mouth.

Procedure

Subjects came to the laboratory on three mornings to participate in sessions lasting approximately 3 h. Following baseline mood and physiological measures, subjects were asked to rate their preference between the regenerated smoke aerosol and the low-nicotine cigarette smoke. In 10 trials, one puff of each type was presented, with order of presentation counterbalanced across trials. Subjects rated how much they liked each puff using a 10-point rating scale.

After this initial preference assessment, subjects were allowed to smoke ad lib, with access to one of the three experimental conditions on a given day (high-nicotine smoke, low-nicotine smoke, regenerated smoke aerosol). All puffs were taken from a clean mouthpiece protruding through an opaque screen. Every hour, the smoke intake monitor filter trap was removed for subsequent weighing. Additional measures of smoke intake consisted of expired air CO concentration (6) and number of cigarettes smoked (every condition presented lit cigarettes but filtered the particulate matter to a different extent). Radial pulse was also counted for 30 s as a functional measure of nicotine absorption. Subjective indices of withdrawal discomfort were also assessed at these times with a smoking withdrawal questionnaire based upon Shiffman and Jarvik (22), which contained seven-point rating scales assessing craving ("Would you like a cigarette?," "Do you miss a cigarette?," "Do you have an urge to smoke?," "Do you crave a cigarette?"); negative affect ("tense," "irritable," and, scored oppositely, "calm," "content"), arousal ("able to concentrate," "wide awake," and, scored oppositely, "unusually sleepy"), and somatic symptoms ("heart beating faster than usual," "fluttery feelings in the chest," "hands shaky," "upset stomach," "heartburn," "feel dizzy," "nauseous").

Data Analysis

Planned comparisons (10) were conducted to address our main hypothesis that the greater sensory impact of the regenerated smoke aerosol relative to the diluted cigarette smoke condition would prevent compensatory increases in smoking behavior usually associated with low-nicotine delivery. Specifically, we predicted subjects would smoke the low-nicotine cigarette more intensively than the regenerated smoke aerosol but that the high-nicotine cigarette would be smoked with comparable intensity to the regenerated smoke aerosol due to their similar sensory impact. Thus, for each dependent measure of smoking behavior the regenerated smoke aerosol condition was compared with the high- and low-nicotine cigarette conditions, using for each comparison a condition (2) $\times$ time (3) repeated-measures analysis of variance (ANOVA). An α criterion of 0.05 (two tailed) was used in all analyses.

Regional airway strength ratings, withdrawal symptoms, and measures of liking and satisfaction obtained from the regenerated smoke condition were also compared to ratings in each of the other two conditions. The low-nicotine cigarette condition was not expected to show any advantage over the regenerated smoke aerosol in terms of these measures despite the expected compensatory smoking of the low-nicotine cigarette.

For the two preference tests, conducted at the beginning and end of each session, an index of preference for regenerated smoke aerosol vs. the low-nicotine cigarette was calculated. This preference index was taken to be the number of puffs for which subjects rated the regenerated smoke as more desirable than the low-nicotine cigarette smoke minus the number of puffs for which subjects rated the regenerated smoke as less desirable than the low-nicotine cigarette. Preference was analyzed in a condition (3) × time (2) repeated-measures ANOVA.

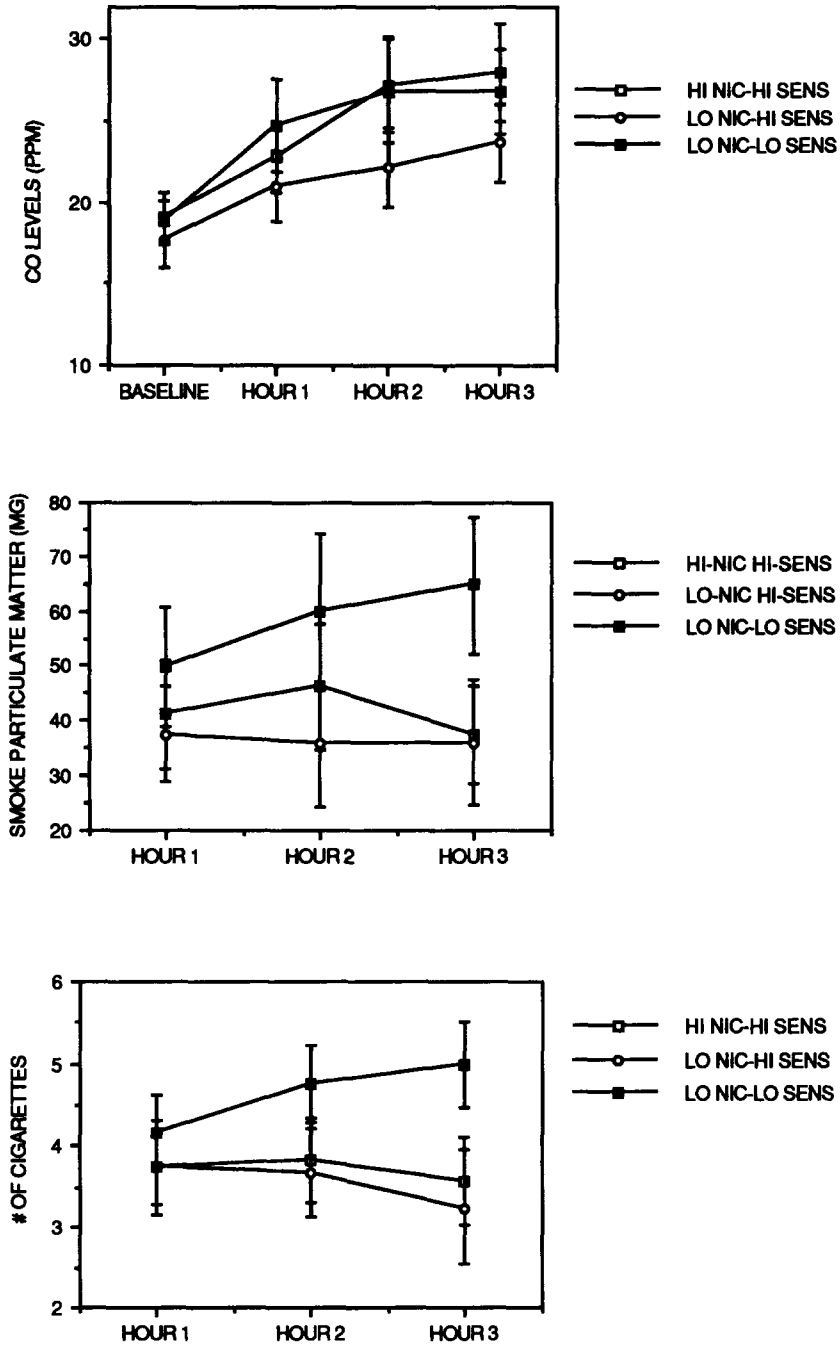

FIG. 4. Measures of smoking intensity (mean ± SEM) in the three experimental conditions. Depicted are expired air carbon monoxide concentrations, mainstream smoke particulate matter, and number of cigarettes smoked. In general, smoking intensity in the low-nicotine, high-sensory condition was comparable to that in the high-nicotine, high-sensory condition, whereas subjects smoked more intensively in the low-nicotine, low-sensory condition.

RESULTS

Smoking Intensity

The main objective indices of smoking intensity were expired air CO, cumulative smoke particulate matter taken from the cigarettes smoked in each hour, and number of cigarettes. Note that these measures did not reflect actual nicotine intake into the mouth but rather the intensity of puffing and inhalation from the cigarettes in each condition. Thus, a high boost in CO in the low-nicotine cigarette condition represented an attempt to inhale more smoke, but the actual nicotine delivered was low because seven eighths of the smoke particulate matter containing nicotine was trapped in a Cambridge filter. The measures of smoking intensity gave a direct measure of compensatory smoking because if the intensity of puffing and inhalation were the same across conditions then these measures would have been similar.

As shown in Fig. 4, the regenerated smoke aerosol was puffed at about equal intensity to the high-nicotine cigarette despite the fact that the nicotine delivered was only 5% of that in the high-nicotine condition. No significant difference in any measure of smoking intensity was detected between the high-nicotine condition and the regenerated smoke condition, $F(1, 11) = 1.92$, $p > 0.15$, for expired air CO, $F(1, 11) = 0.69$, $p > 0.4$, for smoke particulate matter, and $F(1, 11) = 0.22$, $p > 0.6$, for number of cigarettes. However, there were striking differences in smoking intensity between the two low-nicotine conditions, with the low-nicotine cigarette being smoked significantly more intensively than the regenerated smoke aerosol. This was true for expired air CO, $F(1, 11) = 8.3$, $p < 0.02$, smoke particulate matter, $F(1, 11) = 20.95$, $p < 0.001$, as well as for number of cigarettes, $F(1, 11) = 7.03$, $p < 0.03$. For smoke particulate intake, there was also a significant condition × time interaction, $F(2, 22) = 3.47$, $p < 0.05$, due to the increased compensatory smoke intake over time in the low-nicotine cigarette condition (see Fig. 4).

Heart Rate

Unlike the behavioral indices of smoking, heart rate was a measure of actual nicotine intake (23). In the regenerated smoke condition, heart rate was significantly lower overall than in the high-nicotine cigarette condition, $F(1, 11) = 5.73$, $p < 0.05$, for the condition main effect and there was also a nearly significant condition × time interaction, $F(2, 22) = 3.4$, $p = 0.051$, suggesting that the accumulation of nicotine across the session increased the difference in heart rate between these two conditions (see Fig. 5). An analysis of simple main effects at each time point showed that heart rate was significantly greater in the high-nicotine condition at hour 2, $F(1, 11) = 7.8$, $p < 0.02$, and hour 3, $F(1, 11) = 12.67$, $p < 0.01$. Heart rate was also significantly higher in the low-nicotine cigarette condition than in the regenerated smoke aerosol condition, $F(1, 11) = 5.73$, $p < 0.05$. This was suggestive of a higher nicotine intake in the low-nicotine cigarette condition than in the regenerated smoke aerosol condition. There was no condition × time interaction, $F(2, 22) = 0.67$, $p > 0.5$.

Regional Airway Sensation Ratings

There were no differences across conditions in ratings of perceived strength in the nose, tongue, back of the mouth, or chest (all $ps > 0.1$). However, the high-nicotine cigarette was rated as stronger in the windpipe than the regenerated smoke aerosol, $F(1, 11) = 14.31$, $p < 0.01$. Interestingly, perceived strength in the windpipe was also rated significantly higher in the low-nicotine cigarette condition than in the regenerated smoke condition, $F(1, 11) = 5.18$, $p < 0.05$.

Liking and Satisfaction

The high-nicotine smoke was given higher ratings for liking, $F(1, 22) = 22.95$, $p < 0.001$, and satisfaction, $F(1, 22) = 48.9$, $p < 0.001$, than the regenerated smoke condition (see Fig. 6). No significant differences between the regenerated smoke and low-nicotine cigarette were detected in ratings of liking, $F(1, 22) = 2.25$, $p > 0.1$; however, the low-nicotine cigarette was rated as more satisfying, $F(1, 22) = 5.65$, $p < 0.05$. Subjects rated the perceived level of nicotine in the regenerated smoke condition as significantly lower than in the high-nicotine condition, $F(1, 11) = 45.42$, $p < 0.001$, and comparable to that of low-nicotine cigarette condition, $F(1, 11) = 0.29$, $p > 0.2$.

Withdrawal Symptoms

Craving, negative affect, arousal, and somatic symptoms clusters of the withdrawal questionnaire were analyzed.

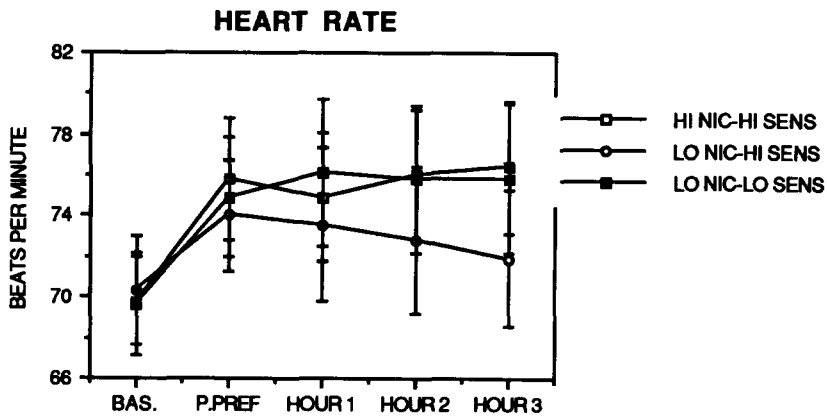

FIG. 5. Heart rate (mean ± SEM) in the three experimental conditions, indicative of lower nicotine intake in the low-nicotine, high-sensory condition.

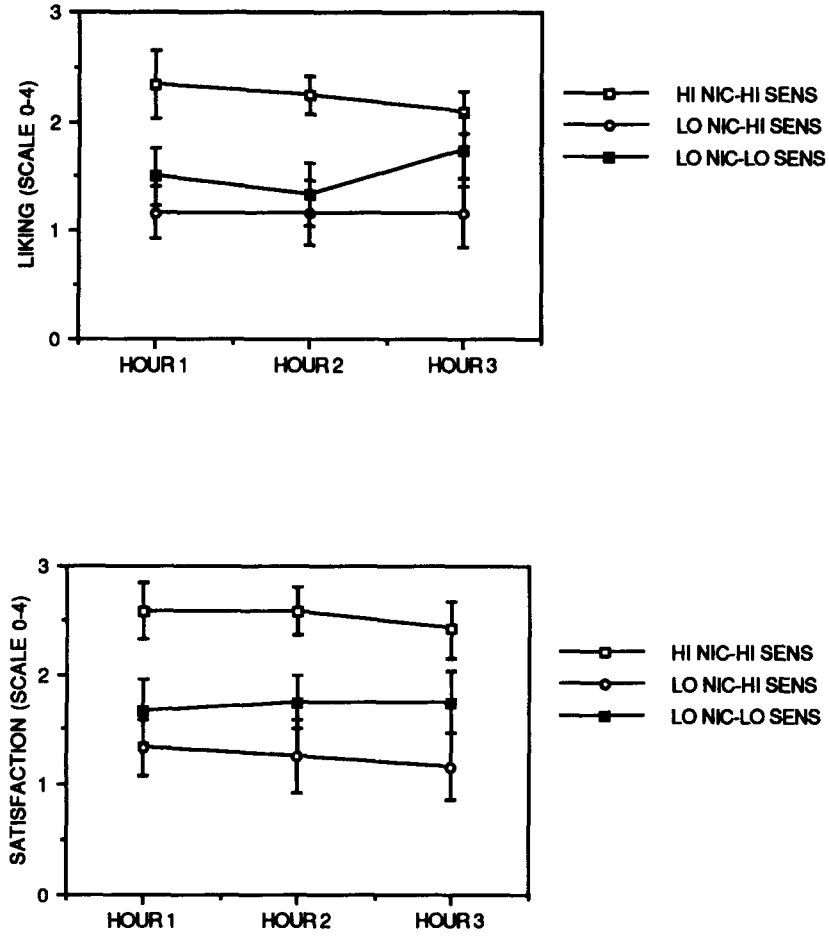

FIG. 6. Subjective ratings of liking and satisfaction (mean ± SEM) for puffs in the three experimental conditions.

Craving for cigarettes was comparable in the high-nicotine cigarette condition and regenerated smoke condition, $F(1, 11) = 1.76, p > 0.2$. In contrast, when comparing craving in the low-nicotine cigarette and regenerated smoke aerosol conditions there was a significant condition × time interaction, $F(2, 22) = 4.26, p < 0.05$. As shown in Fig. 7, this represented a greater reduction in craving over time in the regenerated smoke aerosol condition; at hour 3, the simple main

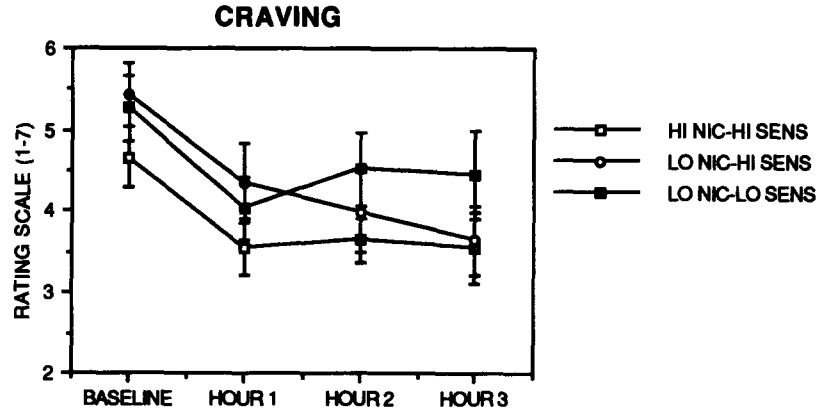

FIG. 7. Subjective craving for cigarettes (mean ± SEM) in the three experimental conditions, showing a marked reduction in craving in the low-nicotine, high-sensory condition, comparable to that in the high-nicotine, high-sensory condition.

effect comparison was marginally significant, $F(1, 11) = 4.45, p < 0.06$.

For negative affect, the comparison of regenerated smoke and high-nicotine cigarette conditions yielded a condition × time interaction that approached significance, $F(2, 22) = 3.19, p = 0.06$; however, none of the simple main effects for each time point were significant (all $ps > 0.09$). There was no difference in negative affect ratings between the regenerated smoke aerosol and low-nicotine cigarette conditions, $F(1, 10) = 0.0, p > 0.9$.

Arousal was significantly greater in the high-nicotine cigarette condition than in the regenerated smoke condition, $F(1, 11) = 6.09, p < 0.05$; there was no difference between regenerated smoke and low-nicotine cigarette conditions, $F(1, 11) = 2.79, p > 0.1$, although there was a trend for lower arousal in the regenerated smoke condition (Fig. 8).

Somatic symptom ratings were not different between conditions (all $ps > 0.2$).

Preference Tests

As described above, preference for the regenerated smoke aerosol vs. the low-nicotine cigarette during the tests at the beginning and end of each session was analyzed in a condition (3) × time (2) repeated-measures ANOVA. There was a condition × time interaction, $F(2, 22) = 3.43$, $p = 0.05$, and therefore the simple main effects at the two time points were analyzed (see Fig. 9). As expected, at the beginning of each session there was no difference between the regenerated smoke condition and the other two conditions in preference for regenerated smoke vs. low-nicotine cigarette smoke, $F(1, 22) = 2.4, p > 0.1$, and $F(1, 22) = 0.07, p > 0.7$, for the comparisons of regenerated smoke day with high-nicotine and low-nicotine cigarette smoke days, respectively. Overall, the regenerated smoke was preferred to low-nicotine cigarette smoke at the beginning of the session; the mean preference index across all conditions was +2.3, significantly greater than the theoretical indifference point of 0 (95% confidence interval around +2.3 is +0.2 to +4.4, which excludes 0). Thus, subjects preferred the regenerated smoke aerosol on an average of two more puffs than they preferred the low-nicotine cigarette. At the end of the session, there was a significant difference in preference for regenerated smoke in the regenerated smoke session vs. the high-nicotine cigarette session, $F(1, 22) = 4.64, p < 0.05$. There was no difference between the regenerated smoke aerosol session and the low-nicotine cigarette session, $F(1, 22) = 1.99, p > 0.1$. Thus, preference for the regenerated smoke tended to decrease from the beginning to the end of the session in which subjects had ad lib access to the regenerated smoke. This change over time was significant, $F(1, 11) = 6.87, p < 0.05$. In contrast, preference for the regenerated smoke tended to increase after exposure to the high-nicotine cigarette condition, although the trend was not significant. In the high-nicotine and low-nicotine cigarette conditions, subjects still preferred the regenerated smoke aerosol at the end of the session whereas at the end of the regenerated smoke session there was neither a preference for nor aversion to the regenerated smoke aerosol relative to the low-nicotine cigarette (see Fig. 9).

DISCUSSION

Our findings demonstrate that smokers regulate their intake of a low-nicotine, high-sensory aerosol much like the smoke from a high-nicotine cigarette. Even though the nicotine intake from the regenerated smoke aerosol was less than 5% of that in the high-nicotine smoke condition, subjects smoked the aerosol to a similar extent, based upon measures of smoke particulate matter, expired air CO, and number of cigarettes. In contrast, subjects appeared to show substantial compensatory increases in smoking the low-nicotine cigarette. Overall, the results indicate subjects responded to peripheral sensory cues in regulating smoke intake and adjusted their smoking behavior to achieve comparable regional airway strength ratings.

During the preference tests, the regenerated smoke aerosol was in general rated as more desirable than the low-nicotine cigarette. However, during the 3-h period of ad lib smoking there was no difference in ratings of liking, and satisfaction was actually slightly higher for the low-nicotine cigarette. Similarly, during the ad lib smoking period ratings of sensory intensity were in general comparable in the low-nicotine cigarette and regenerated smoke aerosol conditions, and the strength in the windpipe was actually higher for the low-nicotine cigarette. These results probably reflect the fact that during the 3 h of ad lib smoking subjects compensated in the low-nicotine cigarette condition by taking larger or more frequent puffs, thereby obtaining a comparable sensory effect to that of the regenerated smoke aerosol condition. In contrast, they would not have been able to compensate effectively for the low-nicotine delivery of the cigarette during the preference tests, in which these puffs were alternated unpredictably

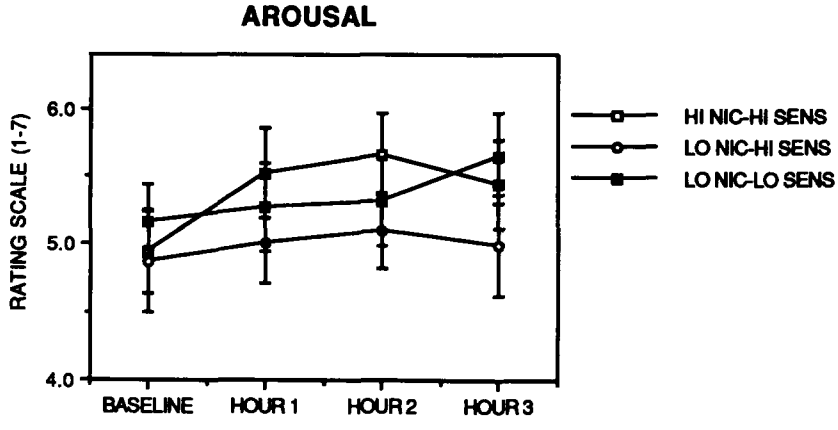

FIG. 8. Subjective arousal (mean ± SEM) in the three experimental conditions.

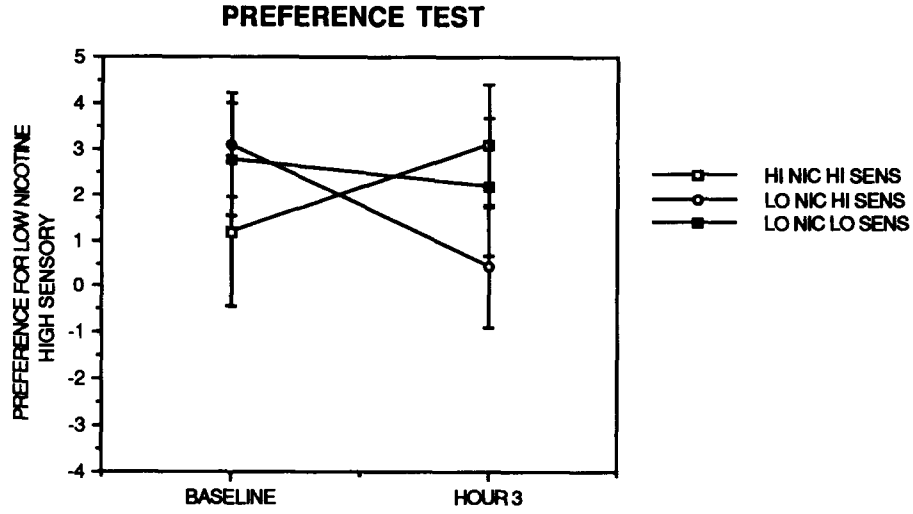

FIG. 9. Preference index for the low-nicotine, high-sensory condition vs. the low-nicotine, low-sensory condition; this index was defined as the differential number of puffs on which the former was rated as more desirable than the latter. The preference index (mean ± SEM) is depicted at baseline and after 3 h of exposure to each condition.

among the stronger-tasting regenerated smoke aerosol puffs. The actual nicotine delivery of a standard puff of the low-nicotine cigarette smoke was somewhat higher than that for an equivalent puff of the regenerated smoke aerosol, and in addition subjects puffed the low-nicotine cigarette smoke more intensively. Thus, subjects required a much higher intake of smoke constituents from the low-nicotine cigarette to match the sensory effects of the regenerated smoke aerosol.

One key advantage of the regenerated smoke aerosol was that it had a strong suppressive effect on craving for cigarettes despite its extremely low-nicotine delivery. Indeed, it was as effective in reducing craving as was the high-nicotine cigarette, replicating our previous findings (2). The mechanism by which the regenerated smoke aerosol reduced craving has not been elucidated. Possibly, the relevant sensory cues have become conditioned reinforcing stimuli because they are usually correlated with nicotine intake and thereby produce a conditioned reduction in the desire to smoke (18). Conceivably, sensory cues could also reduce craving through unconditioned mechanisms involving airway vagal reflexes (7).

However, it is puzzling that, despite the comparable (or higher in the case of windpipe) strength ratings, the low-nicotine cigarette failed to reduce craving to the same extent as the regenerated smoke aerosol. Possibly, craving self-reports are related to the actual intensity of smoking behavior, which was greater in the low-nicotine cigarette condition. Alternatively, the delivery of some nicotine in the low-nicotine cigarette condition may have had a priming effect that tended to elicit craving. Increased smoking of the low-nicotine cigarette resulted in a small, yet significant, increase in nicotine intake (and a tendency for the associated physiological measure of heart rate to increase). Thus, compensatory smoking and higher craving may have been reinforced directly by additional nicotine in the low-nicotine smoke condition. In contrast, the nicotine content of the regenerated smoke aerosol was so low that there may not have been any significant reinforcement for compensatory smoking or craving. This view would predict that smoking of the regenerated smoke aerosol might extinguish faster than that of a low-nicotine cigarette due to the absence of significant nicotine reinforcement, a hypothesis to be tested in future experiments.

The question can be raised as to whether subjects did not compensate with the low-nicotine aerosol because it may have been aversive. Although the regenerated smoke aerosol was rated as significantly less satisfying than the cigarette conditions, the regenerated smoke aerosol was not aversive overall. The preference tests revealed the regenerated smoke aerosol to be rated as *more* desirable than comparable puffs of the low-nicotine cigarette at certain times, and subjects smoked the aerosol in a fashion similar to that of the high-nicotine cigarette. Thus, subjects puffed and inhaled the aerosol to a considerable degree, showed no reduction in smoking the aerosol over the course of the session, and in a previous study we found that a similar aerosol was rated more desirable than control puffs of air (2). However, some subjects did comment that the aerosol had an odd taste. Hence, the aerosol may have presented a mixture of pleasant and aversive cues that was preferable to not smoking at all, and preferable to comparably sized puffs of low-nicotine smoke, but was not as desirable as conventional high-nicotine smoke. While the preference for regenerated smoke over low-nicotine cigarette tended to drop after exposure to the aerosol for 3 h, this may have reflected a partial extinction of its reinforcing value rather than an aversive effect, as mentioned above.

Also relevant to the possible role of aversion in compensatory smoking is the fact that subjects showed compensatory increases in smoking during the low-nicotine smoke condition, even though the desirability of these puffs was less than or equal to that of the aerosol (when evaluated on an equal footing during the preference tests). If low desirability prevents compensation, why would subjects have compensated by smoking more of the low-nicotine cigarette smoke? It is unlikely that lack of desirability per se is the critical determinant of compensation; otherwise, subjects would not have compensated in the low-nicotine smoke condition. The specific sensory effects of the aerosol were probably critical in reducing

craving and preventing compensation; having obtained sufficient airway sensations without compensation, subjects may have wanted to avoid excessive throat harshness that would have accompanied compensatory smoking of the aerosol. This does not mean that the aerosol was aversive as it was actually smoked but only that it provided adequate sensory feedback. This may be analogous to the process whereby smokers limit nicotine intake from cigarettes to avoid toxic symptoms of nicotine overdose. On the other hand, it appears from recent studies of denicotinized cigarettes, which are not at all harsh and yet present similar taste cues as high-nicotine cigarettes, that smokers do not show compensatory increases in smoking these cigarettes (15). Thus, the perception of adequate sensory feedback, whether in the oral or tracheobronchial regions, may be sufficient to limit smoking.

The probable importance of sensory cues in the regulation of smoke intake may help resolve some long-standing puzzles, including the finding that systemically administered nicotine often has less effect on smoking behavior than one might predict. For example, Benowitz and Jacob (4) measured smokers' ad lib nicotine intake from smoking on 1 day and then administered an IV infusion to the same individuals on another day, matching their average level of self-administered nicotine intake. Surprisingly, subjects took in 75% as much nicotine on the day when they received the nicotine infusion as they did on the day they received a saline infusion. Kumar et al. (12) and Lucchesi et al. (14) also found little effect of nicotine on smoking behavior, although sometimes more precise regulation is seen (20). Administration of nicotine via routes other than smoking bypasses the usual respiratory route and its accompanying sensory feedback. Thus, even though smoking withdrawal symptoms may be relieved the usual satiation or metering signals are not provided and because of this smoking behavior may not be inhibited effectively. Russell (21) argued that regulation is much more precise when nicotine is infused rapidly; however, no published study has reported a direct comparison of compensatory changes in smoking behavior in response to fast vs. slow infusions of nicotine. A complicating factor is that rapid nicotine infusions not only produce greater CNS effects but also seem to stimulate lung receptors (7,8). Use of peripheral nicotine antagonists in studies of nicotine regulation could help elucidate the relative contribution of these receptors. One pioneering attempt by Stolerman et al. (24) unfortunately did not establish the absorption or effectiveness of the orally administered peripheral blocker (pentolinium), and therefore follow-up investigations would be most useful.

Of course, sensory effects are not the only relevant influences on smoking reinforcement. One potentially reinforcing effect of the high-nicotine cigarette that was not apparent in the regenerated smoke aerosol condition was an increase in subjective arousal, suggesting that the stimulant effects of nicotine were absent in the aerosol condition. Also, there was a trend for negative affect to be lower in the high-nicotine cigarette condition. A stimulant as well as tension reduction effect could help explain the greater satisfaction attributed to the high-nicotine cigarette. Thus, while sensory factors may be important in the regulation of smoke intake and in craving reduction other reinforcing effects of high doses of nicotine should not be ignored.

Clinically, our results may be relevant to smoking reduction and cessation strategies. To reduce smoking behavior while reducing nicotine and tar intake, it may be helpful to present the usual sensory cues accompanying smoking. For example, it may be fruitful to utilize aerosols that replace the airway stimulation a smoker misses when switching to an alternative form of nicotine replacement such as a transdermal nicotine patch or nicotine chewing gum. We previously found that aerosols presenting citric or ascorbic acids (3,13) can reduce smoking and desire for cigarettes. A second technique that could be helpful is to present a low dose of nicotine in aerosol form, without any tar components that minimize irritation. Under these conditions, it is possible to create a strong sensory impact with an extremely low dose of nicotine. The regenerated smoke aerosol studied here may also be an effective tool for sensory substitution. Techniques yielding low-nicotine delivery with high sensory impact may reduce craving without having a high abuse liability. These strategies as well others could potentially be incorporated into adjuncts for smoking cessation treatment and may increase success rates beyond those seen utilizing existing methods.

ACKNOWLEDGEMENTS

This work was supported by Grant DA 02665 from the National Institute on Drug Abuse and by the Medical Research Service of the Department of Veterans Affairs.

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