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Conditioned Tolerance to the Heart Rate Effects of Smoking

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EPSTEIN, L. H., A. R. CAGGIULA, K. A. PERKINS, S. J. McKENZIE AND J. A. SMITH. *Conditioned tolerance to the heart rate effects of smoking*. PHARMACOL BIOCHEM BEHAV **39**(1) 15–19, 1991.—This study extended our findings that behavioral tolerance to nicotine in animals can be influenced by conditioning to cardiovascular tolerance in humans. Subjects smoked one-half a cigarette during each of five trials. In the ten-minute intersmoking interval the contexts that preceded smoking were varied. Smokers in the Changing group attended to a different five-minute segment of a Sherlock Holmes radio mystery before each trial, while those in the Repeated group listened to the same segment of the tape. Presmoking heart rates were stable across the groups from trials 1 to 5. As predicted, heart rate for subjects who smoked in the same context showed tolerance to smoking from trials 1 to 5 (84.5 to 78 bpm), while subjects who smoked in changing contexts did not develop tolerance (84.8 to 83.9 bpm). COa levels increased equally for both groups over the five trials. The results of this study suggest tolerance to smoking can be influenced by learning.

Smoking Tolerance Conditioning Heart rate

NICOTINE is a sympathomimetic agent that is associated with changes in cardiovascular functioning, including increased heart rate and blood pressure (2,10). Most cardiovascular changes decrease with repeated doses over short intervals, indicative of acute tolerance (2,11). Likewise, chronic tolerance has been observed in individuals with a history of smoking (11).

Recent animal research has shown drug tolerance can be modified by learning (12). We have shown that tolerance to nicotine's elevation of pain thresholds (5) or suppression of food intake in rats (3) is in part learned, as tolerance was disrupted when the environmental conditions that signaled drug administration were changed.

The present study was designed to extend our observations with animals to humans by assessing the effects of smoking context on acute tolerance to cardiovascular effects of smoking and nicotine. Based on conditioning theory (1,12), it was predicted that subjects who repeatedly smoked in an environment that reliably signals smoking should develop tolerance. However, smoking in an environment that changes and does not reliably signal smoking should inhibit the development of tolerance.

METHOD

Subjects

Subjects were 18 male college-aged (20.9 ± 3.0 years, mean $\pm$ S.D.) smokers. They were smoking an average of 19.6 ± 5.7 cigarettes per day with 0.91 ± 0.26 mg/nicotine per cigarette, and had been smoking for 4.4 ± 3.0 years.

Procedure

Each subject participated in one two-hour afternoon session. Subjects smoked ad lib before the session, with subjects smoking from 0 to 9 cigarettes that day (3.9 ± 2.7). Initial alveolar carbon monoxide (COa) levels averaged 22.8 ± 7.8. To keep the time from the last cigarette to the experimental session constant across subjects, each subject smoked one of their own cigarettes upon arriving at the laboratory 30 minutes before the experiment began. Heart rate electrodes were then attached, subjects were provided instructions for the session, and a preliminary COa level taken. The study of subjects in the afternoon, after previous smoking, has the advantage of studying smokers in their typical pattern of smoking, facilitating generalization to normal smoking patterns. However, this procedure has the disadvantage of producing smaller heart rate acceleration than if the subject was studied smoking the first cigarette of the day in the morning.

Subjects were randomly assigned to one of two groups. Each group was presented five smoking trials. Smoking episodes were separated by 10-minute periods, which were divided into two five-minute blocks, with the stimulus context prior to smoking different across the groups. The context prior to smoking was varied for one group (Changing) while the context was kept constant for the other group (Repeated).

In the Changing group no stimuli were presented during the

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TABLE 1

TIMING OF CONDITIONS IN THE EXPERIMENTAL GROUPS

Group	Trial 1			2			3			4			5		
Changing	QU	SH1	SM	QU	SH2	SM	QU	SH3	SM	QU	SH4	SM	QU	SH5	SM
Repeated	QU	SH1	SM	QU	SH1	SM	QU	SH1	SM	QU	SH1	SM	QU	SH1	SM

Note: QU = quiet (i.e., no stimulus presentation), SH(1–5) = the Sherlock Holmes segment being presented; SM = smoking.

Subjects in each group smoked five times, and listened to five segments of Sherlock Holmes and five segments of quiet. The differences across the experimental groups involved the amount of new information presented.

first five minutes of each 10-minute block, and the first five minute segment of a 30-minute Sherlock Holmes radio show (the *Bruce Partington Plans*, starring Basil Rathbone and Nigel Bruce) was played in the second five-minute block. In subsequent trials the 2nd, 3rd, 4th and 5th segments of the mystery story was played. The final 5-minute episode, which included the solution of the mystery, was played after the experiment was completed. Subjects in the Repeated group were provided the same protocol as the Changing group, with the exception that the same five-minute episode of the Sherlock Holmes tape was played prior to each smoking trial. At the end of each segment, subjects were asked a question about the segment to ensure they had attended, and were signalled when to smoke. Thus the amount and type of stimuli presented to subjects prior to smoking in both groups was held constant, but in one group the stimulus required new information processing, while in the other group no new information was presented on each trial. The design for these groups is shown in Table 1.

Smoking

The smoking stimulus involved having subjects smoke their typical cigarette five times, with each smoking trial involving four 4-s puffs taken at 20-s intervals. In order to equate smoking exposure during each trial, subjects smoked according to specific instructions regarding when and how long to puff, and COa levels were monitored after each trial. A new cigarette was used for each dose. The procedure was designed to limit the dose, since Baker and Tiffany (1) have argued that at short interdose intervals associative tolerance is observed more easily with lower drug doses.

At the onset of smoking subjects were instructed to light up their cigarette without inhaling. Five seconds were provided for subjects to light the cigarette and wait for the next instruction. The smoking interval was 81 s, scored from the five seconds preceding smoking, through the 76 seconds that elapsed from inhalation on the first puff to exhalation on the fourth puff.

Measures

COa was measured prior to the experiment and after each smoking episode using standard breath exhalation procedures, and collected in polyvinyl bags (8). COa was used to ensure there was no differential smoke intake across groups which would influence heart rate independently of the environmental manipulations. COa provides an estimate of smoke intake which relates to dosing factors (7). Under normal smoking, COa rises and reaches a steady state, from which future cigarettes will not produce an increase but rather maintain the steady state level. In this study, the COa levels rose equally for both groups on subsequent exposures. COa data from one subject was not usable.

Heart rate was measured by chest electrodes amplified by a Grass 7P4 preamplifier, amplified and displayed on a Grass 7B polygraph. Heart rate was converted to beats per minute (bpm) for the five minutes preceding smoking, the heart rate during the 81 s of smoking, and the five minutes postsmoking. The fifth minute postsmoking preceded the beginning of the five minutes of Repeated or Changing stimuli. Subjects were provided five minutes postsmoking to return to baseline heart rate levels since heart rate changes after nicotine intake are rapid, and usually return to baseline within two to five minutes after smoking (4) or controlled doses of nicotine (11).

RESULTS

The changes in heart rate during smoking across the five trials are presented in Fig. 1. These changes were analyzed using a two-factor mixed analysis of variance, with Group as the between factor and Trials (1–5) as the within factor. To reduce problems resulting from violations in sphericity, multivariate significance levels were reported for this and subsequent analyses for effects involving repeated measures. A significant Group × Trials interaction [Multivariate $F(4,13) = 4.37$, $p = 0.019$] was shown, indicating differences in heart rate by group from

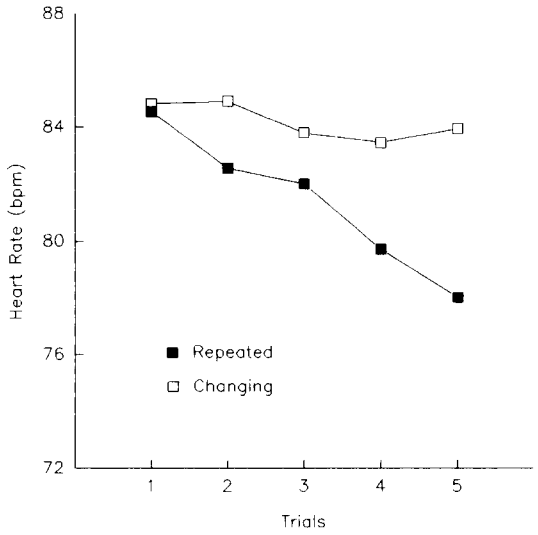

FIG. 1. Heart rate (bpm) during the smoking interval on trials 1 through 5 for subjects in the Changing Stimuli and Repeated Stimuli groups.

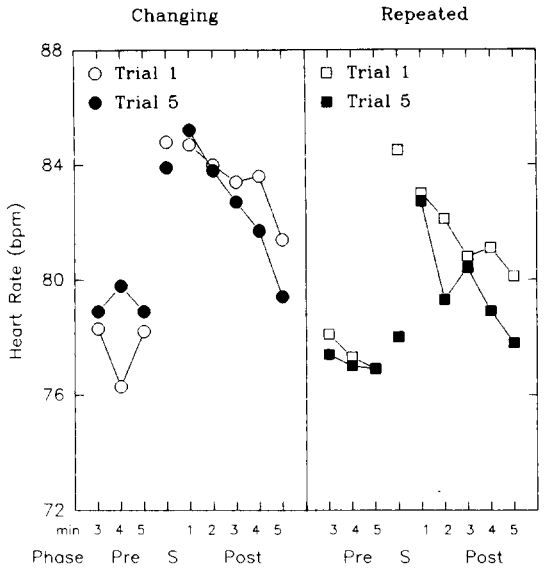

FIG. 2. Heart rate (bpm) during the final three minutes of the Presmoking baseline, Smoking (labeled in the graph as S) and Postsmoking intervals on trials 1 and 5 for subjects in the Changing Stimuli and Repeated Stimuli groups. Significant differences between groups were observed only during the smoking period.

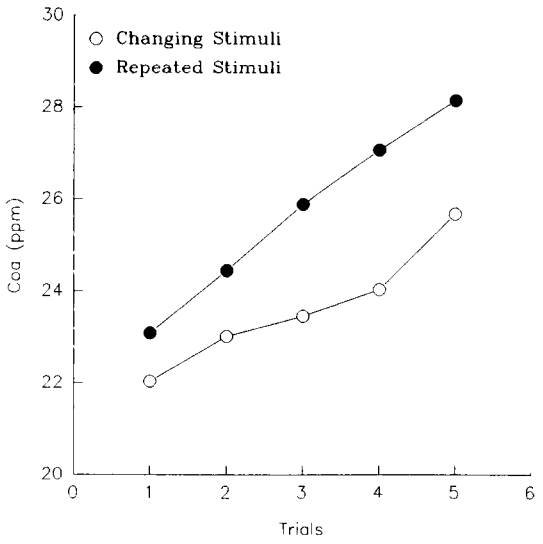

FIG. 3. COa levels (ppm) on trials 1–5 for subjects in the Changing Stimuli and Repeated Stimuli groups.

trials 1 through 5. Tukey post hoc tests showed significant between group differences in heart rate during trials 4 and 5.

A more complete analysis of heart rate for the three minutes before smoking, the smoking period, and the five minutes after smoking is shown in Fig. 2. Heart rate changes were analyzed using a three-factor mixed analysis of variance, with Group as the between factor and Trials (1,5) and Time as the within factors. The analysis was designed to model changes during pre-, smoking and postsmoking by using either heart rate during the minutes 3 and 5 of the presmoking period, the period of smoking administration, and the first and fifth minute after smoking. A significant Group × Trials × Time interaction [Multivariate $F(4,13)=3.84$, $p=0.028$] was shown, indicating differences in heart rate by group over time from trials 1 through 5. A similar analysis using minutes 1 and 5 of the presmoking period, smoking, and minutes 1 and 5 of the postsmoking period was also significant Group × Trials × Time interaction [Multivariate $F(4,13)=3.56$, $p=0.036$].

Tukey post hoc analysis used to assess between group differences across trials and time showed no significant differences in baseline heart rates for trials 1 or 5, suggesting no differences in presmoking heart rate as a function of the different stimulus conditions that preceded the smoking, and that heart rate had returned to presmoking baselines before each smoking episode. Smoking was associated with a significant ($p<0.05$) increase in heart rate during trial 1, and remained significantly elevated ($p<0.05$) from trial 1 to 5 for subjects in the Changing Group, with less than 1 bpm difference from the first to the fifth trial. While heart rate also increased significantly after smoking for subjects in the Repeated Group on trial 1, it decreased from trial 1 to 5, such that at trial 5 heart rate after smoking was no different than before smoking on trial 1. No differences between groups were observed for the five minutes postsmoking.

COa was analyzed using a two-factor analysis of covariance, with Group as the between factor and Trials (1–5) as the within factor. COa on each trial was assessed to ensure that differential intake on trials 2 through 4 did not influence heart rate on Trial 5. Interaction between the covariate and groups was checked to ensure the homogeneity of slopes assumption was met. The COa results (Fig. 3) showed a trend towards increased COa levels across trials [Multivariate $F(4,12)=2.68$, $p=0.08$], but not a significant interaction of Group × Trial [Multivariate $F(4,12)=1.03$, $p=0.43$]. The Repeated group showed a slightly greater increase in COa from trial 1 to 5 than the Changing group, suggesting that differential smoke intake assessed by COa was not the mechanism for the smaller heart rate change observed in the Repeated group.

DISCUSSION

The decreased heart rate to repeated bouts of smoking for subjects in the Repeated group suggests the development of acute tolerance. Tolerance to the heart rate effects of smoking did not develop for subjects who experienced smoking in a context that changed before each smoking bout, suggesting cardiovascular effects of smoking are influenced by the context of drug administration. These results extend our observations on conditioned tolerance in rats (3,5) to humans, and are consistent with previous human research on conditioned tolerance. Payne, Etscheidt and Corrigan (9) provided preliminary evidence for conditioned chronic tolerance in humans to nicotine's effects on heart rate and skin temperature. Using a single subject paradigm the subject alternated smoking on odd numbered days in one context with sham smoking on even numbered days in a second context. After tolerance to smoking had been observed in the first context, the subject then smoked in the second context, and showed recovery of increased heart rate and decreased skin temperature in the environment previously associated with sham smoking. The use of sham smoking in the second environment provided a control for the nonpharmacological cues that may become associated with smoking. Likewise, the use of sham smoking controls in the present study would have provided a test for the role of nicotine versus smoking in the conditioning process. In addition, controls that manipulate the contingency between the conditioning context and the unconditioned smoking stimulus would have provided additional tests for the role of context

in conditioned tolerance.

There are two competing hypotheses that must be ruled out before the role of stimulus cues on tolerance can be supported. First, it is important to consider that the antecedent stimuli (Sherlock Holmes tape) in the Changing group were different over trials, and novelty could have had independent effects on heart rate that contributed to the effects of smoking. Examination of presmoking heart rates for the two groups on trials 1 and 5 showed no differences, and no changes were observed from the end of the post smoking period through the five minutes of the stimulus contexts that signaled smoking. Thus it did not appear that stimulus novelty experienced by the Changing group directly influenced heart rate. In addition, the dose and intersmoking intervals used were designed to produce no difference in presmoking heart rates over trials.

Second, it is also important to rule out differential smoke intake as the mechanism for the heart rate differences between groups. As suggested by the alveolar carbon monoxide levels, the differential heart rate changes were not due to differential nicotine intake across the groups. Direct measurement of serum nicotine would have been preferable to indirect measurement using carbon monoxide. Nevertheless, the number of puffs and puff duration were controlled during each bout. Moreover, the COa boost was slightly greater for the Repeated in comparison to the Changing group, which is exactly the opposite of what would have been expected if differential nicotine exposure was responsible for the lower heart rate response of the Repeated group.

There are two models used to explain the role of context in drug tolerance. The model based on habituation theory states that tolerance will develop when the information about the environment and context of drug delivery matches information about previous doses stored in short term memory. Tolerance will be disrupted when there is a mismatch between the new information presented in comparison to the information stored in short term memory (1,13). Thus tolerance to smoking effects should be more readily observed in environments in which the smoking cues are the same, whereas tolerance will not be observed when the smoking context is changed.

The classical conditioning model (12) states that drug compensatory effects become conditioned to the context of drug delivery, and tolerance will be observed as long as the context of drug delivery remains similar. If the context is changed or becomes unpredictable, then the oppositional process is not elicited and tolerance is not observed. In the present study the pattern of results showed the effects of conditioning were most pronounced for the smoking period, and did not extend to the postsmoking recovery. In fact, examination of the heart rates during and after smoking suggest tolerance was due to an active inhibition of heart rate, as hypothesized in a classical conditioning model, since heart rate after smoking cues were removed was similar to the heart rate observed after the first trial before tolerance had a chance to develop. This may be in part because the different contexts across the two groups were uniquely associated only with the initiation of smoking. After smoking was completed a new set of cues were present, signaled by extinguishing the cigarette. These postsmoking cues were identical across groups, and without distinctive cues for each group conditioned effects might not be expected. If the postsmoking periods were kept different across groups, then the effects of context may have extended to the postsmoking period. The immediate increases in heart rate postsmoking when conditions were changed for the Repeated group also suggests that there was no acute pharmacological tolerance to smoking.

These results have implications for understanding tolerance to the physiological effects of smoking. In the majority of research on acute tolerance to nicotine (2,11), repeated doses are presented in the same environment, which would maximize tolerance being observed. However, in the natural environment, smoking often occurs in changing environments that require rapid information processing, which may minimize the process of tolerance. Thus typical laboratory experiments that provide repeated doses of nicotine in the same environment may overestimate acute tolerance. If changes in the context of drug administration reliably minimize tolerance development, smokers may learn that they can maximize smoking effects by changing the smoking context. This may involve changing the relationship between smoking and behaviors commonly paired with smoking, such as coffee drinking or work.

The doses used may be important in observing conditioning effects. In the present study, subjects smoked one-half cigarette every 10 minutes. While this would result in overall smoking intake similar to that observed for the average smoker in our study (one cigarette every 20 minutes) the dose per cigarette was smaller than typical. The smaller doses may have facilitated the process of conditioning. Baker and Tiffany (1) suggest that conditioned tolerance is more likely to be observed when the drug dose is low, and as dose increases, pharmacological variables become more important. Thus one important component of subsequent research must be the evaluation of the relationship between dose and environmental effects in humans.

Conditioning influences were assessed for one type of acute tolerance, tolerance to the heart rate changes produced by smoking, which may relate to the effects of smoking on cardiovascular disease (6). While we have observed conditioned tolerance to two different behavioral effects in rats (3,5), the effects of conditioning factors should not be generalized to behavioral and subjective tolerance until these other forms of tolerance have been studied.

In summary, we have demonstrated that tolerance to the heart rate effects of nicotine are in part a function of the constancy of the smoking context over trials. As the context changes, the likelihood of observing tolerance decreases. Additional research studying other aspects of the environment and other drug doses is needed to replicate and extend these findings.

REFERENCES

1. Baker, T. B.; Tiffany, S. T. Morphine tolerance as habituation. Psychol. Rev. 92:78–108; 1985.
2. Benowitz, N. L.; Jacob, P.; Jones, R. T.; Rosenberg, J. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. J. Pharmacol. Exp. Ther. 221:368–372; 1982.
3. Caggiula, A. R.; Epstein, L. H.; Stiller, R. Changing temporal cues reduces tolerance to nicotine-induced anorexia. Psychopharmacology (Berlin) 99:389–392; 1989.
4. Cryer, P. E.; Haymond, M. W.; Santiago, J. V.; Shah, S. D. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N. Engl. J. Med. 295:573–577; 1976.
5. Epstein, L. H.; Caggiula, A. R.; Stiller, R. Environment-specific tolerance to nicotine. Psychopharmacology (Berlin) 97:235–237; 1989.
6. Epstein, L. H.; Perkins, K. A. Smoking, stress, and coronary heart disease. J. Consult. Clin. Psychol. 56:342–349; 1988.
7. Henningfield, J. E.; Stitzer, M. L.; Griffiths, R. R. Patterns of carbon monoxide accumulation and elimination as a function of number of cigarettes smoked. Addict. Behav. 5:265–272; 1980.

8. Hughes, J. R.; Frederiksen, L. W.; Frazier, M. A carbon monoxide analyzer for measurement of smoking behavior. Behav. Ther. 9:293–296; 1978.
9. Payne, T. J.; Etscheidt, M.; Corrigan, S. A. Conditioning arbitrary stimuli to cigarette smoke intake: A preliminary study. J. Subst. Abuse 2:113–119; 1990.
10. Perkins, K. A.; Epstein, L. H.; Jennings, J. R.; Stiller, R. The cardiovascular effects of nicotine during stress. Psychopharmacology (Berlin) 90:373–378; 1986.
11. Perkins, K. A.; Epstein, L. H.; Stiller, R.; Marks, B. L.; Jacob, R. G. Chronic and acute tolerance to the heart rate effects of nicotine. Psychopharmacology (Berlin) 97:529–534; 1989.
12. Siegel, S. Classical conditioning, drug tolerance, and drug dependence. In: Israel, Y.; Glaser, F. B.; Kalant, H.; Popham, R. E.; Schmidt, W.; Smart, R. G., eds. Research advances in alcohol and drug problems, vol. 7. New York: Plenum Press; 1983:207–246.
13. Wagner, A. R. Expectancies and the priming of STM. In: Hulse, S. H.; Fowler, H.; Honig, W. K., eds. Cognitive process in animal behavior. Hillsdale: Lawrence Erlbaum; 1978:177–209.