Pharmacology Biochemistry and Behavior, Vol. 45, pp. 375–381, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

Chronic and Acute Tolerance to Subjective Effects of Nicotine

KENNETH A. PERKINS,*[1] JAMES E. GROBE,* LEONARD H. EPSTEIN,* ANTHONY CAGGIULA,‡ RICHARD L. STILLER† AND ROLF G. JACOB*

*Departments of *Psychiatry and †Anesthesiology, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213*
‡Department of Psychology, University of Pittsburgh, Pittsburgh, PA 15260

Received 12 October 1992

PERKINS, K. A., J. E. GROBE, L. H. EPSTEIN, A. CAGGIULA, R. L. STILLER AND R. G. JACOB. *Chronic and acute tolerance to subjective effects of nicotine.* PHARMACOL BIOCHEM BEHAV 45(2) 375–381, 1993.— Tolerance to subjective effects of nicotine may induce novice smokers to increase the magnitude and frequency of their nicotine self-dosing. In this study, smokers (n = 8) and nonsmokers (n = 7) participated in three sessions involving presentation of 0, 7.5, or 15 μg/kg nicotine 30 min for 2 h via measured-dose nasal spray, with different doses presented on separate days. Subjective responses were assessed using visual analog scales (VASs) of jittery, light-headed, relaxed, dizzy, and head rush, and the Profile of Mood States (POMS) scales of vigor, confusion, fatigue, tension, and the composite scale of arousal. Smaller responses in smokers vs. nonsmokers were viewed as evidence for chronic tolerance. In addition, on each day subjects received a fifth, challenge dose of 30 μg/kg 30 min after the previous dosing. Smaller responses to the challenge dose as a function of increasing prior nicotine dosing during Trials 1–4 were viewed as evidence for acute tolerance. Results showed significant changes in most measures as a function of nicotine dose, and the dose–response curves for most VAS and POMS scales tended to be shifted to the right, or dampened, in smokers relative to nonsmokers, consistent with chronic tolerance. However, smokers and nonsmokers tended to respond to nicotine in opposite directions for POMS scales of vigor and arousal, perhaps reflecting withdrawal relief in smokers. Acute tolerance on a few selected VAS and POMS scales was apparent for both smokers and nonsmokers. These results support the notions that chronic use of nicotine is associated with chronic tolerance to some subjective effects of nicotine and that repeated nicotine exposure during a single day elicits progressively smaller responses on selected measures.

Nicotine Smokers Nonsmokers Subjective responses Tolerance

NICOTINE is the main psychoactive substance in tobacco that reinforces smoking behavior (23). As with other drugs of abuse, the subjective effects of nicotine may be critical to its reinforcing efficacy (6), although nicotine's potential effects on enhancing cognitive and behavioral performance may also be involved (23). One view of the onset of regular smoking suggests that repeated exposure to nicotine gradually leads to reduced magnitude of its effects (23), including subjective effects. This reduction in drug effects with increasing drug exposure is termed chronic tolerance (10). The onset of chronic tolerance to nicotine may subsequently lead to greater smoking in an effort by the smoker to continue to obtain the same magnitude of reinforcing effects of nicotine. Repeated exposures to nicotine during the course of a single day (i.e., individual cigarettes) may also lead to reduced responding across these exposures, a change that may reflect acute tolerance (10). Research on chronic and acute tolerance to subjective effects of nicotine may provide directions for the study of tobacco dependence (1), as well as increase our understanding of long- and short-term adaptation to nicotine intake.

We are aware of little controlled human research that has specifically examined chronic and acute tolerance to subjective effects of nicotine, perhaps because of methodological limitations with most available methods of nicotine administration. Presentation of nicotine via smoking is imprecise (7), even across exposures within subjects, and is difficult and noxious for nonsmokers. Presentation of nicotine via gum or transdermal patch is also somewhat imprecise and, importantly, fails to reproduce the rapid uptake of bolus nicotine that is observed with cigarette smoking and may be essential to its reinforcing efficacy (18). However, one recent study did find increased light-headedness and nausea in nonsmokers vs. smokers receiving the same amount of nicotine via transdermal patch (21).

Using a measured-dose nasal spray dosing procedure devel-

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

oped in our lab (13), we investigated differences in subjective responses to nicotine as a function of smoking status, reflecting chronic tolerance, and amount of immediately preceding nicotine exposure, reflecting acute tolerance (10). Use of this method is important because it provides reliable and rapidly absorbed doses. It also allows us to isolate the specific subjective effects of nicotine per se without the effects of nonpharmacological as well as other pharmacological aspects of smoking. In addition, separating nicotine administration from the stimuli typically accompanying it in smoking (e.g., sight, smell, and taste of smoke) minimizes the possibility that any tolerance shown by smokers is conditioned tolerance (4) and therefore allows us to examine unconditioned, pharmacological tolerance in a fairly clean fashion. We previously employed this method to examine chronic and acute tolerance to cardiovascular effects of nicotine in smokers (14,17) and differences in behavioral performance effects of nicotine between smokers and nonsmokers (15).

METHOD

Subjects

Subjects in this study were eight smokers and eight nonsmokers (four male, four female in each group). Mean ± SE ages were 20.4 ± 0.5 years for smokers and 23.7 ± 0.9 for nonsmokers. Smokers reported smoking a mean of 22.4 ± 2.4 cigarettes per day for 2.3 ± 0.4 years and had a Fagerstrom Scale score of 5.3 ± 0.7 (5). Mean nicotine yield of preferred brand was 0.8 ± 0.1 mg. One male nonsmoker was subsequently eliminated from analyses after he admitted regular use of smokeless tobacco, leaving seven nonsmokers who denied past or current regular use of tobacco (i.e., less than 20 cigarettes/lifetime).

Subjective Measures

One-hundred-millimeter visual analog scales (VASs) of "jittery," "dizzy," "light-headed," "relaxed," and "head rush." These were developed on the basis of previous research on the positive and aversive effects of nicotine (23).

Profile of Mood States [POMS; (11)] scales of vigor, confusion, fatigue, and tension, as well as the composite scale of arousal [(vigor + tension) − (confusion + fatigue); see deWit et al. (3)]. The POMS has been used widely in studies of the subjective effects of abused drugs (3), including nicotine (12).

Procedure

Subjects participated in three morning sessions, each after overnight abstinence from smoking (expired-air carbon monoxide <13 ppm), caffeine, and food. During each session, subjects initially completed subjective measures after resting quietly for 30 min (predrug baseline). Subjects were then administered 0, 7.5, or 15 μg/kg nicotine in double-blind fashion via measured-dose nasal spray once every 30 min for 2 h (total of four presentations of assigned dose per session). For the average subject, the higher dose of 15 μg/kg is similar to the typical amount of nicotine absorbed by smokers after smoking one cigarette [approximately 1.0 mg (23)]. Details of this nicotine dosing procedure have been described previously (13–15). Doses were presented on separate days, and the order of doses across days was counterbalanced. Subjective measures were obtained within 5 min of each dose administration. Smaller responses in smokers vs. nonsmokers would suggest chronic tolerance to nicotine in smokers (i.e., resulting from their extensive experience with nicotine via past smoking history).

In addition, on each day smokers and nonsmokers subsequently received a fifth, challenge trial involving administration of 30 μg/kg nicotine 30 min after Trial 4. One female nonsmoker was unable to complete all of the challenge trials for each day due to nausea, leaving complete data from the challenge trial for six nonsmokers. It was hypothesized that smaller responses to the challenge dose as a function of increasing prior exposure to nicotine during Trials 1–4 would be evidence for acute tolerance. In other words, responses of subjects to the 30-μg/kg challenge would be smaller on the days they previously received 7.5 or 15 μg/kg during Trials 1–4, compared with the day they previously received 0 μg/kg during Trials 1–4. [This design, based upon the classic animal research of Stolerman et al. (22), was thought to provide a methodologically strong test of acute tolerance since it avoids confounding the manipulation of prior nicotine exposure with time. One typical way of assessing acute tolerance, especially in human research, is to observe a decline in response from the first to the last presentation of the same dose (14). However, that procedure does not account for the possibility that a number of factors unrelated to drug exposure can produce, or prevent, a decline in responding over time with successive drug presentations, such as fatigue or circadian changes. Our design avoids this complication because the challenge dose is presented at the same time point in the session for all prior dosing conditions.]

Finally, to determine whether magnitude of responses to nicotine observed in nonsmokers could be elicited in smokers by higher nicotine doses, also consistent with the notion of tolerance (10), smokers of this study subsequently participated in a fourth, exploratory session after completing the three sessions involving 0-, 7.5-, and 15-μg/kg dosing. During this last session, smokers received four administrations of 30 μg/kg nicotine, one every 30 min for 2 h as in the previous sessions involving the lower doses. These responses were not included in analyses because there were no comparable values for nonsmokers, but were plotted in figures to provide additional information on the responses of smokers to a fuller range of doses.

Data Analyses

Responses to nicotine were analyzed by two separate 2 × 3 mixed analyses of variance (ANOVAs), each with one between-subjects factor (smokers vs. nonsmokers) and one within-subjects factor (nicotine dose: 0, 7.5, and 15 μg/kg). The dependent measure for the first ANOVA was mean change from baseline to Trials 1–4. It was hypothesized that smaller responses in smokers would indicate chronic tolerance. The dependent measure for the second ANOVA was mean change from baseline to the fifth, challenge trial involving 30 μg/kg. Smaller responses to the challenge trial following larger doses presented in Trials 1–4 would suggest acute tolerance. (Gender was not included as a second between-subjects factor due to the relatively small n for each group, but gender was controlled by providing equal representation of males and females between groups.) Pair-wise comparisons between smokers and nonsmokers (chronic tolerance) and between challenge dose responses following 7.5 or 15 μg/kg vs. 0 (acute tolerance) were performed using Fisher's least significant difference t-test (9).

RESULTS

Chronic Tolerance

There were no significant differences between smokers and nonsmokers in predose baseline values on any of the VAS scales. As shown in Fig. 1, ANOVA results revealed that nicotine significantly increased in dose-dependent fashion the VAS scales of light-headed, $F(2, 26) = 9.15$, $p < 0.001$, jittery, $F(2, 26) = 3.90$, $p < 0.05$, dizzy, $F(2, 26) = 4.62$, $p < 0.02$, and head rush, $F(2, 26) = 7.92$, $p < 0.005$, and marginally decreased the VAS scale of relaxed, $F(2, 26) = 3.17$, $p < 0.06$. Further, the dose-response curves for smokers tended to be shifted to the right and/or dampened, providing evidence of chronic tolerance (10). However, responses of smokers were significantly smaller, relative to those of nonsmokers, only for light-headed and dizzy (Fig. 1).

Nicotine also increased the POMS scales of confusion, $F(2, 26) = 8.68$, $p < 0.001$, and fatigue, $F(2, 26) = 2.96$, $p < 0.07$, in dose-dependent fashion (Fig. 1). As with VAS scale results, the dose-response curves for smokers on confusion and fatigue were dampened and/or shifted to the right, consistent with chronic tolerance, although responses of smokers on both measures were significantly smaller only following the 7.5-μg/kg dose. Results for POMS-tension were similar, as responses of smokers were smaller following both the 7.5- and 15-μg/kg doses. Responses on other POMS scales of vigor and arousal were somewhat different, as nonsmokers experienced a significant decrease in both due to nicotine, while smokers showed little change or an increase. This differential direction of response was most apparent for vigor, as the status × dose interaction approached significance, $F(2, 26) = 3.14$, $p = 0.06$.

The apparent differential direction of response to nicotine as a function of smoking status may be related to the differences in baseline levels on these particular measures. Smokers had significantly lower baseline levels of vigor, $F(1, 13) = 5.36$, $p < 0.05$, and arousal, $F(1, 13) = 9.83$, $p < 0.01$, and higher levels of fatigue, $F(1, 13) = 6.73$, $p < 0.05$, than nonsmokers, possibly because of tobacco withdrawal due to the required overnight abstinence from smoking. Thus, relative to placebo nicotine tended to increase smokers' low baseline levels of vigor and have little effect on arousal and fatigue, while nicotine decreased nonsmokers' relatively high baseline levels of arousal and vigor and increased their low levels of fatigue.

Acute Tolerance

Responses to the 30-μg/kg challenge dose were influenced by the dose presented during the preceding Trials 1–4 for only some measures, as shown in Fig. 2. Consistent with acute tolerance, challenge trial responses were significantly smaller with increasing dose during Trials 1–4 for VAS scales of dizzy, $F(2, 24) = 5.98$, $p < 0.01$, and head rush, $F(2, 24) = 6.56$, $p = 0.005$, less so for light-headed, $F(2, 24) = 2.71$, $p < 0.09$, and not influenced by Trials 1–4 dosing for relaxed, $F(2, 24) = 2.41$, $p > 0.10$, and jittery, $F(2, 24) = 1.78$, $p > 0.10$. However, pair-wise comparisons revealed that acute tolerance to dizzy and head rush responses was significant only for nonsmokers, perhaps due in part to their greater initial responsivity to nicotine relative to smokers (Fig. 1).

As with the results for Trials 1–4 (chronic tolerance), a somewhat different pattern of responses to the challenge dose emerged for the POMS scales. Smokers tended to show acute tolerance to nicotine-induced increases in arousal and to decreases in fatigue, while nonsmokers tended to show little acute tolerance to nicotine-induced changes in these measures, which were opposite in direction to those of smokers (Fig. 2). This differential responding is supported by the significant status × dose interactions for arousal, $F(2, 24) = 4.23$, $p < 0.03$, and fatigue, $F(2, 24) = 5.47$, $p = 0.01$. Although responses to POMS scales of vigor, confusion, and tension appeared to show acute tolerance, these results were not significant [main effect of dose for POMS-tension, $F(2, 24) = 2.89$, $p < 0.08$.

Finally, the main effect of smoking status on responses to the challenge dose was significant or nearly significant for the VAS scales of jittery, $F(1, 12) = 3.11$, $p = 0.10$, light-headed, $F(1, 12) = 3.41$, $p < 0.10$, and dizzy, $F(1, 12) = 13.79$, $p < 0.005$, and the POMS scales of arousal, $F(1, 12) = 24.27$, $p < 0.001$, confusion, $F(1, 12) = 9.19$, $p = 0.01$, fatigue, $F(1, 12) = 6.91$, $p < 0.05$, tension, $F(1, 12) = 3.62$, $p < 0.10$, and vigor, $F(1, 12) = 16.63$, $p < 0.005$. These differences between smokers and nonsmokers in subjective responses to the 30-μg/kg nicotine challenge supplement the findings from Trials 1–4, above, that the responses of smokers to measured amounts of nicotine are smaller than those of nonsmokers, consistent with chronic tolerance.

DISCUSSION

The results of this preliminary study suggest that smokers show chronic tolerance to subjective effects of nicotine per se, separate from any subjective effects of nonnicotine constituents of tobacco smoking. These findings complement previous research by us (14) and others (21) in strengthening support for the existence of chronic tolerance to effects of nicotine in humans. They also build on animal research demonstrating tolerance to nicotine's discriminative stimulus effects (24), which may parallel its subjective effects in humans, as well as tolerance to other effects of nicotine (1). Thus, this research is consistent with the notion that chronic exposure to nicotine can lead smokers to experience less subjective effects from smoking. Such chronic tolerance could encourage an increase in nicotine self-dosing, assuming some of these or similar subjective effects are reinforcing. A complete discussion of potential mechanisms to explain chronic tolerance to subjective effects of nicotine is beyond the scope of this article. However, it is likely that long-term nicotine exposure in smokers leads to more modest neurochemical changes associated with its subjective effects or less responsivity to these changes via alterations in nicotine receptor sensitivity (1). These responses probably involve catecholaminergic and cholinergic activity, as well as a number of other possible discriminable substances in the CNS (1).

There was also evidence of acute tolerance to some of these subjective effects of nicotine in both smokers and nonsmokers, extending to subjective responses previous research showing acute tolerance to cardiovascular effects of nicotine in smokers (14,17) and nonsmokers (12,19). The presence of acute tolerance in nonsmokers suggests that novice smokers may be able to adapt rapidly to some of the initially marked effects of nicotine during a smoking episode, perhaps leading to increased ability to smoke more than one cigarette per episode. It is likely that mechanisms involved in acute tolerance to nicotine involve short-term changes in receptor sensitivity, although little research has examined this question.

It is conceivable that factors other than long-term nicotine

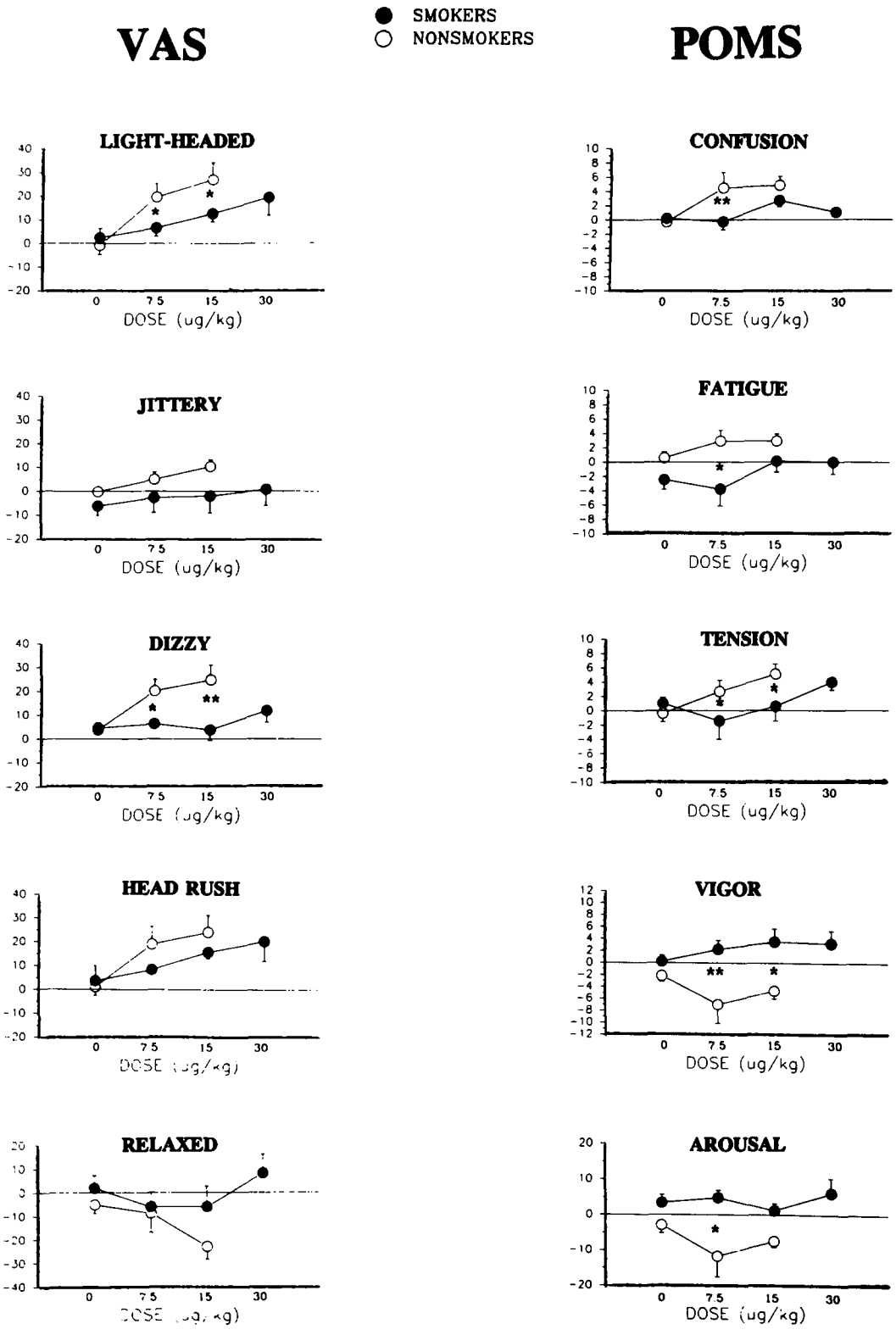

FIG. 1. Mean ± SEM change in VAS and POMS subjective measure scores from predose baseline following 0, 7.5, and 15 μg/kg nicotine in smokers and nonsmokers (and 30 μg/kg nicotine for smokers only). Maximum possible ranges of change in scores are −100 to 100 for VAS scales, −28 to 28 for POMS-confusion and POMS-fatigue, −36 to 36 for POMS-tension, −32 to 32 for POMS-vigor, and −124 to 124 for the composite scale of POMS-arousal. Responses averaged over dose Trials 1–4. *$p < 0.05$, **$p < 0.01$, for differences between groups.

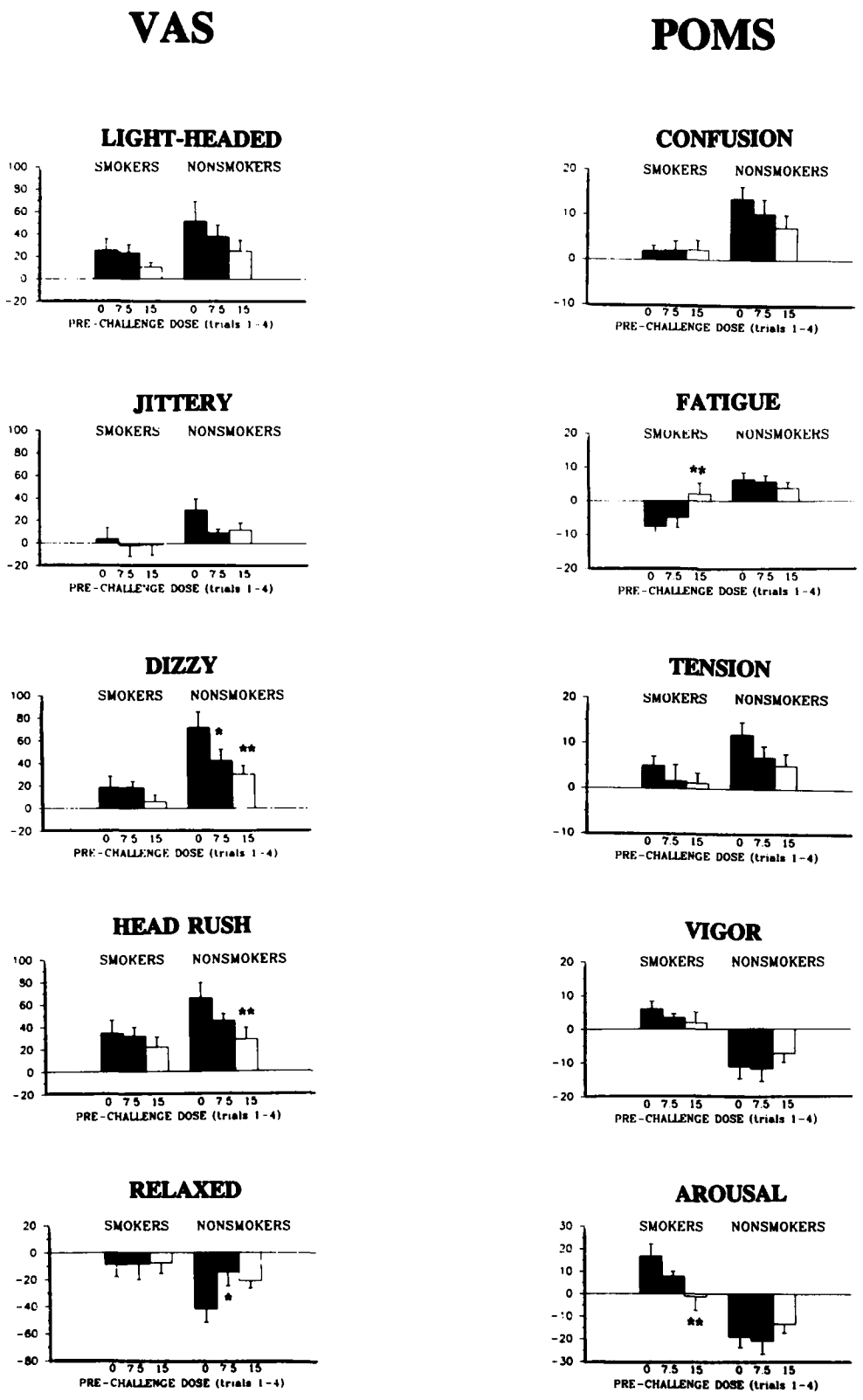

FIG. 2. Mean ± SEM change in VAS and POMS subjective measure scores from predose baseline to the 30-μg/kg challenge trial as a function of Trial 1–4 dosing with 0, 7.5, and 15 μg/kg nicotine in smokers and nonsmokers. Maximum possible ranges of change are same as in Fig. 1. *$p < 0.05$, **$p < 0.01$, for differences between 7.5 or 15 μg/kg vs. 0.

exposure could explain the differences in response to nicotine between smokers and nonsmokers because humans are not randomly assigned to nicotine histories but self-select their exposure. Smokers could be constitutionally different from nonsmokers in important ways that influence the manner in which they respond to nicotine (8). Thus, smokers may have responded less markedly on measures such as POMS-tension and confusion and VAS dizzy and light-headed because of an innate insensitivity to less pleasant effects of nicotine rather than tolerance due to chronic exposure. It is interesting that nicotine produced changes in nonsmokers that could be viewed as aversive (e.g., increased tension and confusion, decreased vigor), similar to a recent study of IV nicotine effects in nonsmokers (12). These results call into question whether nicotine actually has direct reinforcing effects on mood in inexperienced users (8). It may be that nicotine intake via smoking produces substantially different, and perhaps more positive, subjective effects, but we previously observed virtually identical subjective arousal effects of nasal nicotine spray and controlled tobacco smoking in smokers (16), similar to another study comparing IV and smoked nicotine (6). In any case, additional research is needed to help determine the likelihood that a possible constitutional difference explains the different magnitude of subjective responses between smokers and nonsmokers.

It is also possible that tobacco withdrawal due to overnight abstinence was responsible for some of the differential responding, especially the different direction of some responses to nicotine in smokers vs. nonsmokers. There was a significant baseline difference between smokers and nonsmokers on POMS scales of vigor, fatigue, and arousal, and nicotine tended to produce responses on these measures that were opposite in direction from baseline levels (i.e., increase in the group with lower baseline, decrease in the group with higher baseline). However, chronic tolerance was observed here for other measures on which there was no baseline difference. Also, in a previous study we observed a similar mediating influence of baseline on subjective arousal responses to both nicotine and smoking among smokers (16). In that study, smokers with high baseline arousal showed no change while smokers with low baseline arousal showed a large increase, and this difference was unrelated to history of smoking exposure. Therefore, tobacco withdrawal is unlikely to be the sole explanation for the differential responding due to smoking status.

Subsequent research is needed with larger samples to replicate these findings and determine whether the chronic tolerance observed here is functional or is due to differences between smokers and nonsmokers in pharmacokinetics of nicotine after absorption [i.e., dispositional tolerance; (2,10)]. This research should also broaden the scope of nicotine effects to behavioral and cognitive responses to determine the extent to which chronic and acute tolerance to nicotine occurs and whether this tolerance is general or specific to particular response domains. Separate manipulation of nonnicotine stimuli [e.g., sight of smoke; (20)] may help determine the contribution of conditioned stimuli to tolerance to nicotine via tobacco smoking in smokers. Studies examining differences in tolerance as a function of dependence are needed to help ascertain whether nicotine tolerance and tobacco dependence are linked (1). Finally, longitudinal research assessing responses to nicotine during the adoption of regular smoking and following cessation of smoking could help determine the rate of development and the rate of decay, respectively, of chronic tolerance to nicotine.

ACKNOWLEDGEMENTS

This research was supported by Grant DA-05807 from the National Institute on Drug Abuse. The authors thank Annette Scierka, Rena Solberg-Kassel, Celeste Elash, and William Reynolds for their able assistance.

REFERENCES

1. Balfour, D. J. K. The neurochemical mechanisms underlying nicotine tolerance and dependence. In Pratt, J. A., ed. The biological bases of drug tolerance and dependence. New York: Academic Press; 1991:121–151.
2. Benowitz, N. L.; Jacob, P. Nicotine and cotinine elimination kinetics in smokers and nonsmokers. Clin. Pharmacol. Ther. (in press).
3. DeWit, H. J.; Pierri, J.; Johanson, C. E. Reinforcing and subjective effects of diazepam in nondrug-abusing volunteers. Pharmacol. Biochem. Behav. 33:205–213; 1989.
4. Epstein, L. H.; Caggiula, A. R.; Stiller, R. Environment-specific tolerance to nicotine. Psychopharmacology (Berl.) 97:235–237; 1989.
5. Fagerstrom, K. O. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict. Behav. 3:235–241; 1978.
6. Henningfield, J. E.; Miyasato, K.; Jasinski, D. R. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J. Pharmacol. Exp. Ther. 234:1–12; 1985.
7. Herning, R. I.; Jones, R. T.; Benowitz, N. L.; Mines, A. H. How a cigarette is smoked determines blood nicotine levels. Clin. Pharmacol. Ther. 33:84–90; 1983.
8. Hughes, J. Distinguishing withdrawal relief and direct effects of smoking. Psychopharmacology (Berl.) 104:409–410; 1991.
9. Huitema, B. E. Analysis of covariance and alternatives. New York: John Wiley & Sons; 1980.
10. Kalant, H.; LeBlanc, A. E.; Gibbins, R. J. Tolerance to, and dependence on, some nonopiate psychotropic drugs. Pharmacol. Rev. 23:135–191; 1971.
11. McNair, D. M.; Loor, M.; Droppelman, L. F. Profile of mood states. San Diego, CA: Educational and Testing Service; 1971.
12. Newhouse, P. A.; Sunderland, T.; Narang, P. K.; Mellow, A. M.; Fertig, J. B.; Lawlor, B. A.; Murphy, D. L. Neuroendocrine, physiologic, and behavioral responses following intravenous nicotine in nonsmoking healthy volunteers and in patients with Alzheimer's disease. Psychoneuroendocrinology 15:471–484; 1990.
13. Perkins, K. A.; Epstein, L. H.; Stiller, R.; Jennings, J. R.; Christiansen, C.; McCarthy, T. An aerosol spray alternative to cigarette smoking in the study of the behavioral and physiological effects of nicotine. Behav. Res. Meth. Instrum. Comput. 18:420–426; 1986.
14. Perkins, K. A.; Epstein, L. H.; Stiller, R. L.; Marks, B. L.; Jacob, R. G. Chronic and acute tolerance to the heart rate effects of nicotine. Psychopharmacology (Berl.) 97:529–534; 1989.
15. Perkins, K. A.; Epstein, L. H.; Stiller, R. L.; Sexton, J. E.; Debski, T.; Jacob, R. G. Behavioral performance effects of nicotine in smokers and nonsmokers. Pharmacol. Biochem. Behav. 37:11–15; 1990.
16. Perkins, K. A.; Grobe, J. E.; Epstein, L. H.; Caggiula, A. R.; Stiller, R. L. Effects of nicotine on subjective arousal may be dependent on baseline subjective state. J. Subst. Abuse 4:131–141; 1992.
17. Perkins, K. A.; Stiller, R. L.; Jennings, J. R. Acute tolerance to

the cardiovascular effects of nicotine. Drug Alcohol Depend. 29: 77–85; 1991.
18. Russell, M. A. H.; Feyerabend, C. Cigarette smoking: A dependence on high-nicotine boli. Drug Metab. Rev. 8:29–57; 1978.
19. Russell, M. A. H.; Jarvis, M. J.; Jones, G.; Feyerabend, C. Non-smokers show acute tolerance to subcutaneous nicotine. Psychopharmacology (Berl.) 102:56–58; 1990.
20. Saumet, J. L.; Dittmar, A. Heat loss and anticipatory finger vasoconstriction induced by a smoking of a single cigarette. Physiol. Behav. 35:229–232; 1985.
21. Srivastava, E. D.; Russell, M. A. H.; Feyerabend, C.; Masterson, J. G.; Rhodes, J. Sensitivity and tolerance to nicotine in smokers and nonsmokers. Psychopharmacology (Berl.) 105:63–68; 1991.
22. Stolerman, I. P.; Bunker, P.; Jarvik, M. E. Nicotine tolerance in rats: Role of dose and dose interval. Psychopharmacologia 34: 317–324; 1974.
23. US DHHS. The health consequences of smoking: Nicotine addiction. Washington, DC: US Government Printing Office; 1988.
24. Young, A. M. Tolerance to drugs acting as discriminative stimuli. In Glennon, R. A.; Jarbe, T. U. C.; Frankenheim, J., eds. Drug discrimination: Applications to drug abuse research. NIDA Research Monograph 116. Washington, DC: US Government Printing Office; 1991:197–211.