Pharmacology Biochemistry & Behavior Vol 38, pp 333–337 © Pergamon Press plc, 1991 Printed in the U S A 0091-3057/91 $3 00 + 00

Psychophysiological Interactions Between Caffeine and Nicotine

JED E. ROSE[1] AND FREDERIQUE M. BEHM

Nicotine Research Laboratory, VA Medical Center, Durham, NC and Department of Psychiatry, Duke University, Durham, NC

Received 16 July 1990

ROSE, J E AND F M BEHM. *Psychophysiological interactions between caffeine and nicotine* PHARMACOL BIOCHEM BEHAV **38**(2) 333–337, 1991 —The interactive effects of caffeine and nicotine were studied in twelve subjects. Mood and physiologic responses to the pharmacologic components nicotine and caffeine were measured, while controlling for the sensory/behavioral aspects of smoking and coffee drinking Two experimental sessions presented a caffeine × nicotine design, with caffeinated or decaffeinated coffee followed at thirty-minute intervals by controlled inhalations of nicotine and nonnicotine smoke Results showed that there was a significant interactive effect of caffeine and nicotine on subjective arousal such that nicotine decreased arousal only in the presence of caffeine These findings extend previous work showing interactive effects of caffeine and self-titrated doses of cigarette smoke in affecting subjective arousal The effects of nicotine on subjective arousal may, therefore, depend not only on nicotine dose, but also on the presence of caffeine Heart rate was increased by nicotine and both systolic and diastolic blood pressures were elevated by caffeine Caffeine also potentiated the increase in diastolic blood pressure resulting from smoke inhalations, but this occurred irrespective of nicotine dose

Nicotine Cigarette smoking Caffeine Coffee Arousal Cardiovascular

CAFFEINE and nicotine are two of the most ubiquitous drugs used in society, and they are frequently consumed together Epidemiologic and laboratory studies suggest that the concurrent administration of nicotine (usually in cigarette smoke) and caffeine (usually in coffee) is not merely coincidental. Cigarette smokers consume more coffee than nonsmokers, and cigarettes tend to be preferentially consumed during coffee drinking (7, 8, 14). One possible factor accounting for this link between cigarette and coffee consumption is the shorter half-life of caffeine in smokers, requiring a greater dose of caffeine to produce a given effect (3). However, this factor alone does not account for the temporal contiguity between coffee and cigarette consumption (14). A second explanation is that the same factor triggers both behaviors, e.g , stress or work breaks A third explanation is that caffeine and nicotine interact pharmacologically such that an effect is obtained from combined use that is different from that obtained from either alone In a previous study (15), we found that cigarette smoking prevented the increase in subjective arousal caused by prior administration of 150 mg caffeine. If caffeine affects the response to nicotine, then an investigation of possible mechanisms may reveal factors which contribute to the maintenance of cigarette smoking and which may lead to relapse after smoking cessation

The present study was designed to extend the findings of our previous study in two ways. The prior study allowed subjects to adjust their own smoke intake, and, therefore, more nicotine may have been inhaled in the caffeinated coffee condition. Indeed, changes in expired CO levels after smoking were higher in the caffeine condition, indicating greater smoke inhalation (2). Thus the differential effect of smoking after caffeinated as opposed to decaffeinated coffee administration may have been due to a biphasic dose-response effect of nicotine, with low doses of nicotine increasing arousal and higher doses exerting a sedative effect (1). The prior study also compared the effects of smoking with a no-smoking control condition; hence, this manipulation of nicotine delivery did not control at all for the sensory and behavioral aspects of smoking. Therefore, in the present study we compared the effect of controlled inhalations of nicotine-containing smoke with inhalations of nonnicotine smoke

METHOD

Subjects

Twelve smokers (7 women, 5 men), with a mean age of 42.2 years (s.d. = 15.54), were recruited from local community newspaper advertisements. To be eligible for the study, subjects had to report smoking at least 20 cigarettes and drinking at least 3 cups of caffeinated coffee per day. Subjects reported smoking an average of 26.5 cigarettes per day (s.d. = 8.29), having an estimated nicotine delivery (by FTC analysis) of 1.0 mg (s d =0 2). Subjects' average total daily intake of caffeine from brewed cof-

[1]Requests for reprints should be addressed to Dr Jed E Rose, Nicotine Research Laboratory (151-S), VA Medical Center, 508 Fulton St , Durham, NC 27705

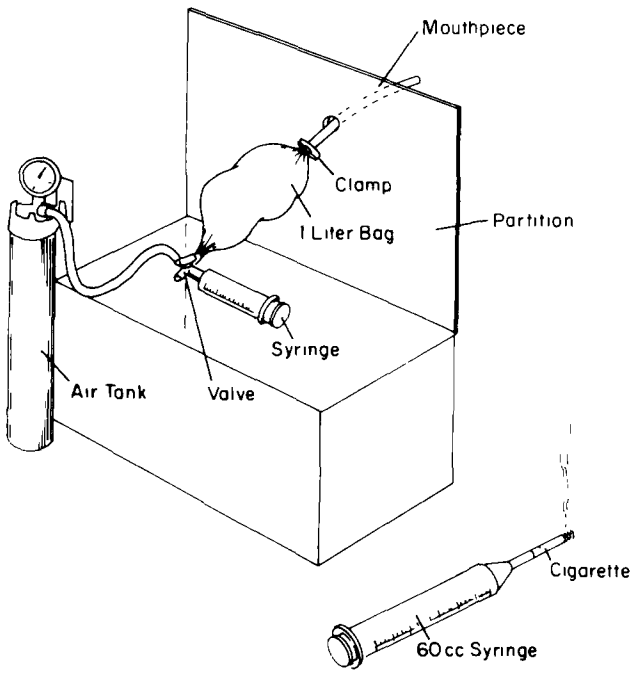

FIG 1 Apparatus used to present controlled puff and inhalation volumes of cigarette smoke.

fee, instant coffee, tea and/or caffeinated colas was 641 mg (s.d. = 182 mg), corresponding to 5–6 cups of strong brewed caffeinated coffee The Fagerstrom tolerance questionnaire was administered over the telephone to assess subject's nicotine dependence. The Eysenck Personality Inventory (5) was also administered in the first session, in order to assess extraversion and neuroticism, two personality dimensions which have been reported to correlate with caffeine and nicotine effects (4). Subjects were told that the purpose of the study was to examine interactions between coffee and cigarettes, and were paid $8/h for their participation.

Apparatus

The controlled volumes of cigarette smoke, diluted in air, were administered through a mouthpiece protruding from an opaque screen. A Marlboro cigarette was used in the nicotine-containing smoke conditions, and a Triumph tobacco-free cigarette was used in the nonnicotine control conditions. Prior to each of the 15 puffs delivered in both conditions, a one-liter bag was mechanically inflated with a measured volume of air from a pressurized air tank. A 35 cc puff from either a Triumph or a Marlboro cigarette was then drawn into a plastic syringe, half of the volume of smoke was expelled, and the remaining 17.5 cc was injected into the bag (see Fig. 1). To minimize smoke deposition or coagulation of smoke particulates in the apparatus, subjects were immediately asked to inhale the smoke/air mixture from the mouthpiece and hold their breath 3 s. The use of a relatively small puff volume and the dilution with air were necessary to minimize subjects' ability to distinguish between the sensory cues of the Triumph and the Marlboro smoke. Based on published values for the nicotine delivery of the tobacco cigarette used, the 15 inhalations would have delivered a maximum of 0.75 mg nicotine, which is comparable to that usually obtained from smoking a typical cigarette. The actual nicotine dose delivered was probably somewhat less than 0 75 mg due to some nicotine and smoke particulates being deposited on the walls of the apparatus.

Coffee Preparation

Caffeinated coffee was prepared by adding 15 cc of a solution containing 150 mg of caffeine base to a cup containing 150 cc of decaffeinated coffee (98% caffeine free). The decaffeinated condition presented a cup containing 150 cc of decaffeinated coffee The taste and aroma of caffeinated and decaffeinated coffee were indistinguishable at this concentration (10)

Physiologic Measurements

Skin temperature. Skin temperature was taken by having the subject hold a probe between the index finger and thumb of the right hand for 4 seconds, using a Digital Thermometer (Fisher Model RTD with probe ranging from −100 to 850°C).

Carbon monoxide analysis Expired air carbon monoxide (CO) measurements were performed by having subjects hold their breath for 15 seconds, discard the first portion of the expirate to eliminate dead space air, and blow into a balloon for analysis using an Ecolyzer (Model 211) CO analyzer.

Heart rate Heart rate was measured by counting the radial pulse for 1 minute

Blood pressure. Systolic and diastolic blood pressure readings were taken manually using a sphygmomanometer.

Subjective Mood

The two main mood dimensions measured were Arousal and Tension. Arousal was assessed with three items taken from the Profile of Mood States questionnaire (12) "awake," "lively" and (scored oppositely) "tired." Tension was assessed with the two items "tense" and "jittery " For each item, subjects rated themselves for how they felt "right now," using a scale ranging from 0 ("not at all") to 4 ("extremely"). The sums of the scores for all items in a given dimension were used in the data analyses.

Craving for Cigarettes

Craving for cigarette smoke was assessed using two items from the Shiffman-Jarvik Smoking Withdrawal Scale (16): "Would you like a cigarette?" and "Do you miss a cigarette?" Subjects used a 0 to 4 scale for each item, and the scores were added to obtain an overall rating of craving.

Sensory Evaluation Questionnaire

A puff rating sheet was used having 0 to 4 rating scales with the following items "Flavor/aroma strength," "Throat harshness," "Strength in chest," "Lightheadedness," "Satisfaction," "Nicotine content "

Procedure

Subjects were tested two at a time and each subject came to the laboratory for two morning sessions. They were instructed to abstain from caffeine and nicotine since the previous night and were told that upon arrival to the laboratory they would be tested for both caffeine and nicotine, using saliva and breath samples. On the day of the session, after giving their informed consent, subjects filled out questionnaires evaluating their subjective mood

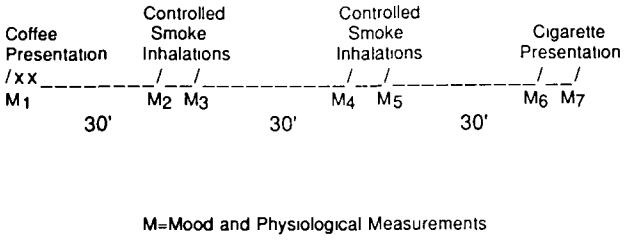

FIG 2 Timeline showing sequence of events in the experimental sessions

(see below), caffeine consumption and smoking habits, and the Eysenck Personality Inventory was administered

Then subjects were given their first of seven sets of measurements (see Timeline, Fig 2). Each set of measurements consisted of a mood questionnaire, followed by measurement of skin temperature, heart rate, blood pressure and expired air carbon monoxide concentrations. Upon completion of the first set of measurements, subjects drank a cup of coffee (either caffeinated or decaffeinated coffee). After a 30-minute wait to allow for caffeine absorption, during which subjects sat quietly in the waiting area with magazines and newspapers available, a second set of measurements was taken. This was immediately followed by smoke administration. Fifteen smoke inhalations were given, with a 30-s interval between inhalations. Each set of inhalations was administered using puffs from either a Triumph (nonnicotine) or Marlboro (nicotine) cigarette, using the inhalation apparatus described above (each puff being diluted with 1 liter air to minimize the sensory cues) Measurement set No. 3 ensued, followed by another 30-minute rest period. Smoking was not permitted during the rest period, and subjects were told to restrict their interaction by not talking with each other. After the 30 minutes, measurement set No. 4 was administered, followed by another 15 inhalations of either the Triumph or the Marlboro cigarette smoke, whichever had not been administered during the first set of inhalation. Measurement No. 5 was taken immediately after the smoke inhalations and was followed by another 30-minute rest. Then, measurement set No. 6 was taken and both smokers were allowed to smoke a Marlboro cigarette normally, without the use of any apparatus. A final set of measurements (set No 7) was then taken.

On the second day, the same timeline was used but the caffeine condition was changed (caffeinated vs. decaffeinated). The order of smoke type (Triumph/Marlboro vs. Marlboro/Triumph) and coffee type was counterbalanced across subjects

Data Analysis

The main hypothesis of the study was that caffeine would modulate the effect of nicotine on arousal. The effect of each set of smoke inhalations on arousal was defined as the difference between pre- and postsmoking values of arousal, the immediate change in arousal after smoke inhalation, as opposed to the final level, was of primary interest because of possible carryover effects from the smoking condition presented 30 minutes earlier. A 2 (Nicotine) × 2 (Caffeine) ANOVA was conducted on this change in arousal in the four different experimental conditions (nicotine containing smoke/caffeinated coffee; nicotine containing smoke/decaffeinated coffee; nonnicotine smoke/caffeinated coffee; nonnicotine smoke/decaffeinated coffee). ANOVA's were also conducted on the effect of smoke inhalations on tension and physiological indices (heart rate, blood pressure and skin temperature) The criterion for significance was alpha = 0.05. Pending a significant interaction, simple main effects of nicotine in each caffeine condition were evaluated (9).

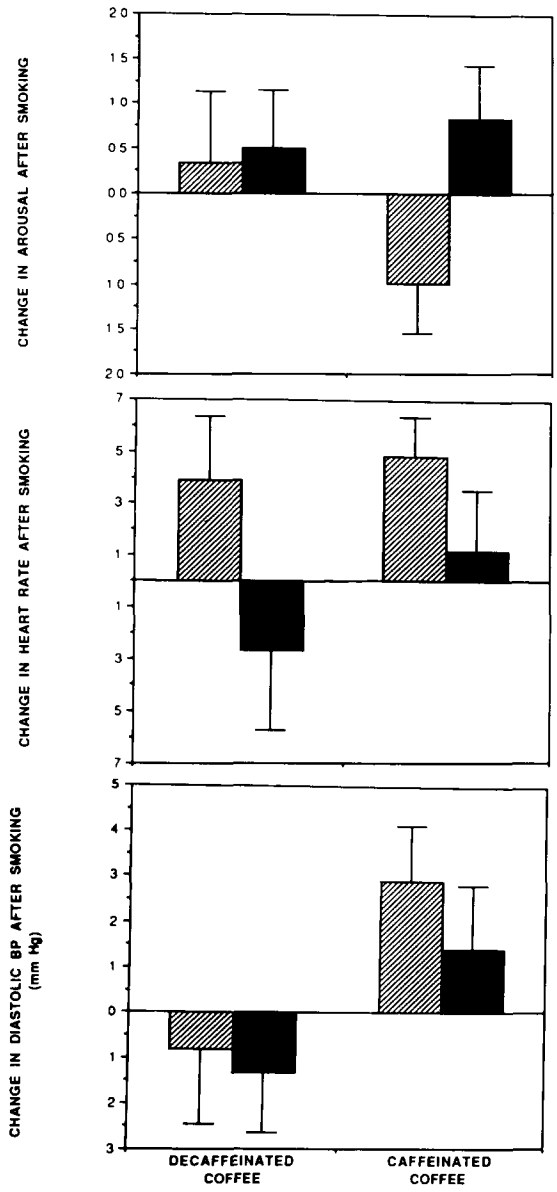

FIG 3 Change (±s e m) in self-reported arousal, heart rate, and diastolic blood pressure after inhalations of nicotine-containing or nonnicotine smoke, subjects having previously consumed caffeinated or decaffeinated coffee Hatched bars nicotine, solid bars nonnicotine

Mood Variables

The analyses conducted on the change in arousal after smoking showed a significant interaction between nicotine and caffeine, $F(1,11) = 6.06$, $p < 0.03$ As shown in Fig. 3, this was due to the fact that the nicotine-containing smoke reduced subjective arousal relative to the nonnicotine smoke in the caffeinated coffee condition, but not in the decaffeinated coffee condition An

analysis of the simple main effects of nicotine confirmed that there was a significant effect of nicotine in the caffeinated coffee condition ($p<0.02$) but not in the decaffeinated coffee condition ($p=0$ 81). Mean arousal prior to smoking in the four conditions was 4.4 (s.d. = 2.11) for nicotine smoke/caffeinated coffee; 3 4 (s.d. = 3.23) for nicotine smoke/decaffeinated coffee, 3 5 (s.d. = 2 68) for nonnicotine smoke/caffeinated coffee; and 4.0 (s.d. = 2.98) for nonnicotine smoke/decaffeinated coffee. These values were not significantly different, as assessed by a Caffeine × Nicotine ANOVA (all p's>0.05). Tension was not significantly affected by nicotine or caffeine, and there was no interaction (all p's>0.1)

Physiological Variables

Nicotine caused a significant elevation in heart rate of approximately 5 bpm (see Fig. 3); $F(1,11)=6.63$, $p<0.03$ for the main effect of nicotine. No effect of caffeine, $F(1,11)=1.33$, $p=0.27$, or significant interactive effects of caffeine and nicotine, $F(1,11)=0.24$, $p=0.63$, were detected Heart rate prior to smoke inhalations was similar in all conditions and averaged 72 bpm (s.d. = 10.8) in the nicotine smoke/caffeinated coffee condition; 72 bpm (s d = 11.9) in the nicotine smoke/decaffeinated coffee condition; 74 bpm (s.d. = 11.0) in the nonnicotine smoke/caffeinated coffee condition, and 75 bpm (s.d. = 13.1) in the nonnicotine smoke/decaffeinated coffee condition. These values did not differ significantly from each other. The change in systolic blood pressure showed no effect of either drug and no interaction (all p's>0.5), but the diastolic blood pressure response to smoke inhalations was increased by caffeine [$F(1,11)=6.49$, $p<0.03$ for the main effect of caffeine, see Fig. 3]. There was no main effect of nicotine, $F(1,11)=0.39$, $p=0.55$, and no caffeine × nicotine interaction, $F(1,11)=0.1$, $p=0.76$ Mean diastolic blood pressure before smoking was 78 mmHg (s d = 12.7) in the nicotine smoke/caffeinated coffee condition, 74 mmHg (s.d = 10.6) in the nicotine smoke/decaffeinated coffee condition, 80 mmHg (s.d. = 8.83) in the nonnicotine smoke/caffeinated coffee condition, and 75 mmHg (s.d. = 9.8) in the nonnicotine smoke/decaffeinated coffee condition. An ANOVA conducted on these presmoking values showed a highly significant main effect of caffeine on diastolic blood pressure, $F(1,11)=9.83$, $p<0$ 01. There was no effect of nicotine, $F(1,11)=0$ 54, $p=0$ 48, and no interaction, $F(1,11)=0$ 01, $p=0.92$. Systolic blood pressure was also elevated in the caffeine condition prior to smoking [$F(1,11)=7.99$, $p<0$ 02 for the main effect of caffeine]. The change in skin temperature after smoke inhalations was not affected by nicotine [$F(1,11)=1.6$, $p=0.23$ for the main effect of nicotine], but there was a nonsignificant trend for caffeine to potentiate the decrease in skin temperature observed after smoke inhalations [$F(1,11)=3$ 37, $p=0.09$ for the main effect of caffeine]. There was no caffeine × nicotine interaction, $F(1,11)=2.18$, $p=0$ 17.

Efficacy of Controlled Smoke Inhalation System

Based on expired air CO measurements taken before and after each set of smoke inhalations, the smoke delivery system was effective at equating smoke inhalation in the caffeinated and decaffeinated coffee conditions The mean rise in CO was 7 6 ppm in the nicotine-caffeinated coffee condition and 7.2 ppm in the nicotine-decaffeinated coffee condition. The corresponding changes in expired air CO for the nonnicotine smoke conditions were 6 ppm (caffeine) and 4.5 ppm (no caffeine). A Caffeine × Nicotine ANOVA revealed a significant main effect for smoke type, with the nicotine-containing cigarettes delivering slightly more CO, $F(1,11)=6$ 48, $p<0$ 03; there was no difference between expired CO change in the caffeinated and decaffeinated coffee conditions, $F(1,11)=1.48$, $p=0.25$ and no caffeine × nicotine interaction, $F(1,11)=0.63$, $p=0$ 44.

Sensory ratings of the strength and harshness of smoke in each condition supported the view that a small puff volume and dilution of smoke in air minimized the distinguishability of the nicotine and nonnicotine smoke. None of the ratings of strength, satisfaction, nicotine content or lightheadedness differed between Marlboro and Triumph conditions (all p's>0.1). Moreover, the reduction in reported craving (desire) for cigarettes was very similar in all smoking conditions [$F(1,11)=0$, $p=1.0$ for the main effect of nicotine; $F(1,11)=0.43$, $p=0.53$ for the main effect of caffeine; and $F(1,11)=2$ 90, $p=0.12$ for the caffeine × nicotine interaction]

Personality

In the decaffeinated coffee condition, there was a significant positive correlation (r = .58) between Eysenck Personality Inventory scores for extraversion and the effect of nicotine on arousal in the decaffeinated coffee conditions No significant correlations were found for the effect of nicotine in the caffeine condition. Also, there was no significant correlation between extraversion and the effects of caffeine on arousal, assessed as the difference between self-reported arousal in the caffeinated and decaffeinated coffee conditions, measured 30 minutes after coffee administration and before smoke administration.

Effects of Caffeine on Responses to Ad Lib Smoking

A comparison of the effects of the Marlboro cigarette smoked at the end of the session in the caffeinated and decaffeinated coffee conditions was conducted, using paired t-tests. None of the subjective or physiological changes showed an effect of caffeine at this time, approximately 2½ h after caffeine administration.

DISCUSSION

The findings from this study replicate and extend our previous results showing that, under at least a limited range of circumstances, caffeine and nicotine interact in affecting subjective arousal The present findings suggest that the arousal-reducing effects of cigarette smoking in the presence of caffeinated vs. decaffeinated coffee are not due solely to a higher dose of nicotine being taken in after caffeinated coffee, for smoke inhalations were controlled. Moreover, the effects of smoking on arousal were not due solely to sensorimotor factors, as these were equated by the use of a nontobacco smoke control, in conjunction with smoke dilution to mask the sensory differences between nicotine and nonnicotine smoke. Therefore, the results support a pharmacological interaction between the psychoactive constituents caffeine and nicotine in the laboratory environment used. This environment was relatively unstimulating, and it remains to be seen whether similar interactive effects of nicotine and caffeine are observed in more naturalistic environments or in situations generating high arousal.

Differential effects of nicotine on arousal, depending on preexisting state, have been reported previously by Mangan and Golding (13) Measuring EEG activation, they found that nicotine exerted a stimulant effect when subjects were in a low arousal situation, but had a depressant effect when subjects were in a stressful condition. Neither nicotine dose nor sensory factors were rigorously controlled in that study. Our results complement these findings by showing that the presence of caffeine may modulate the effects of nicotine in a similar fashion to other environmental sources of arousal The positive correlation between extraversion and the effects of nicotine on arousal support Eysenck's theory (4), which states that extraverts are cortically underaroused and derive primarily a stimulant effect from nicotine Introverts are hypothesized to derive a reduction in arousal from smoking Ey-

senck and O'Conner (6) reported findings consistent with these predictions. In contrast, in a study of individuals classified as either smoking predominantly in high or low arousal situations, Suraway and Cox (17) found no effects of smoking on arousal. However, in that study, subjects were asked to abstain from caffeinated beverages. It may be worthwhile to examine the different effects of nicotine on these types of smokers when they are given caffeine.

The behavioral significance of the caffeine-nicotine interaction reported here has not been identified, and it is not known whether it may help explain the frequently observed concurrent use of caffeine and nicotine. Possibly, a cigarette-related decrease in arousal could be desirable in situations in which there are few active responses available The effects of caffeine on the subjective response to nicotine differed markedly from its effects on physiological and subjective reactivity to smoke inhalations. Caffeine augmented diastolic blood pressure increases, and possibly skin temperature decreases, after smoke inhalations. These effects were not dependent on the actions of nicotine, but occurred in both nicotine and nonnicotine smoke conditions. The physiological effects of caffeine in potentiating physiological responses to stressful tasks have been shown previously (11). In contrast, the effects of caffeine on subjective arousal showed a specific interaction with nicotine. Further research will be necessary to examine the subjective as well as physiological interactions between caffeine and nicotine under a wider range of doses and environmental conditions.

ACKNOWLEDGEMENTS

This research was supported by grant DA 02665 from the National Institute on Drug Abuse and by the Medical Research Service of the Veterans Administration

REFERENCES

1 Ashton, H , Milman, J E., Telford, R. E , Thompson, J W The effect of caffeine, nitrazepam and cigarette smoking on the contingent negative variation in man Electroencephalogr Clin Neurophysiol 37 59–71, 1974
2 Colletti, G , Supnick, J A , Abueg, F. R Assessment of the relationship between self-reported smoking rate and ecolyzer measurement. Addict Behav 7 183–188, 1982
3 Emurian, H , Nellis, M J , Brady, J V., Ray, R L Event time-series relationship between cigarette smoking and coffee drinking Addict. Behav 7 441–444, 1982
4 Eysenck, H J Personality and maintenance of the smoking habit In Dunn, W L , ed Smoking behaviour Motives and incentives Washington V H Winston, 1973.
5 Eysenck, H J , Eysenck, S B G Manual of the Eysenck Personality Questionnaire (junior and adult) San Diego, CA Holder and Stoughton, 1975
6 Eysenck, H J , O'Conner, K Smoking, arousal and personality In Remond, A , Izard, C , eds Electrophysiological effects of nicotine Amsterdam Elsevier/North Holland, 1979 147–157
7 Hrubec, Z Coffee drinking and ischaemic heart disease Lancet 1 548–549, 1978
8 Istvan, J , Matarazzo, J D Tobacco, alcohol and caffeine use A review of their interactions Psychol Bull 95 301–326, 1984
9 Keppel, G Design and analysis Englewood Cliffs, NJ Prentice-Hall, Inc , 1982 214–215
10 Kozlowski, L T Effects of caffeine consumption on nicotine consumption Psychopharmacology (Berlin) 47 165–168, 1976
11 Lane, J D , Williams, R B. Caffeine affects cardiovascular responses to stress Psychophysiology 22 648–655, 1985
12 McNair, D M , Loor, M , Droppleman, L F Profile of Mood States San Diego, CA Educational and Testing Service, 1971
13 Mangan, G. L , Golding, J F The psychopharmacology of smoking Oxford Cambridge University Press, 1984 127
14 Parsons, W D , Neims, A H Effects of smoking on caffeine clearance Clin Pharmacol Ther 24 40–45, 1978
15 Rose, J E Cigarette smoking blocks caffeine-induced arousal Alcohol Drug Res 7 49–55, 1986
16 Shiffman, S M , Jarvik, M E Smoking withdrawal symptoms in two weeks abstinence Psychopharmacology (Berlin) 50 35–39, 1976
17 Suraway, C , Cox, T Smoking behaviour under conditions of relaxation A comparison between types of smokers Addict Behav 11 187–191, 1986