PHARMACODYNAMICS AND DRUG ACTION

Effects of tobacco smoking on human ocular smooth pursuit

Objective: Test the hypothesis that nicotine-induced nystagmus results in reduced ocular smooth performance and pupil diameter in tobacco smokers.

Methods: Twenty nonsmokers (age range, 20 to 45 years; mean age ± SE, 31.5 ± 1.7 years) and 14 smokers (age range, 17 to 50 years; mean age ± SE, 30.6 ± 2.6 years) were studied after a minimum of 2 hours of tobacco abstinence. Subjects were studied before and immediately after they inhaled air through a sham cigarette or after they smoked one of their preferred brand of cigarettes, respectively.

Results: A very small, consistent, and statistically significant increase in smooth pursuit was found with both eyes to a 15 degrees per second moving target after one tobacco cigarette was smoked. This was due to improvement in left and not right eye smooth pursuit. The nonsmokers had no significant change in 15 degrees per second pursuit after sham smoking. Nonsmokers and smokers did not differ in left eye 6 degrees per second smooth pursuit before or after sham or tobacco smoking. The changes in right eye 6 degrees per second smooth pursuit were inconsistent and differed at various times between the two groups. During the smooth pursuit task the pupil diameter of the nonsmokers increased, but there was no change in the tobacco smokers. Black subjects had smaller baseline pupils than white subjects, unrelated to smoking status.

Conclusions: Contrary to the hypothesis, tobacco smokers had a very small but significant improvement in left eye pursuit but no change in pupil diameter. Race-related differences in baseline pupil diameter were similar in both nonsmokers and smokers. (Clin Pharmacol Ther 1997;61:349-59.)

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Smoking a tobacco-containing cigarette is a highly efficient method of delivering nicotine into the lungs and, thus, very rapidly throughout the body, including the brain. Tobacco smoke, although containing many chemicals, is a convenient way to study the pharmacologic effects of nicotine in humans. In view of the relative lack of knowledge on the functions of nicotinic cholinergic receptors in the brain, studies of the short- and long-term effects of tobacco smoke on nervous system functions are of scientific importance unrelated to issues of the acknowledged harmful effects of tobacco smoking. Understanding the function of the nicotinic cholinergic system may shed light on why some people smoke tobacco.

Ocular tracking of a smoothly moving target has been used to study a variety of psychoactive drugs.[1,2] Two kinds of eye movements are involved in tracking. One is smooth pursuit and the other is abrupt saccades. Different but interactive brain systems are involved.[3] The smooth pursuit system is especially useful to predict where a target is going, based on where it has been. Smooth pursuit is used to maintain an image of a smoothly moving target on the fovea, whereas saccades bring the target image onto the fovea. Both the smooth pursuit and the saccadic

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ocular motor systems contribute to the performance of a pursuit task. Many psychoactive drugs, especially sedative-hypnotics such as ethyl alcohol, disrupt pursuit performance in which smooth pursuit appears to be more sensitive than saccades.[3] In contrast, a dose of 20 mg amphetamine, given subcutaneously to each of 20 normal subjects, increased the number of "catch-up" saccades and maintained smooth pursuit through most of the target range. Tedeschi et al.[4] reported that 15 mg amphetamine, given orally to five normal volunteers, had no effect on smooth pursuit velocity, peak saccadic velocity, or duration, but the same dose given intravenously to a different group of six volunteers prevented the fatigue of repeated testing on peak saccadic velocity and duration.

Inasmuch as nicotine-induced nystagmus is a well-known phenomenon, the working hypothesis of this research was that ocular smooth pursuit would be altered in smokers immediately after a cigarette was smoked. Sibony et al.[5] reported that smoking a single cigarette caused an increase in saccadic intrusions during smooth pursuit tasks including "catch-up," "jump back," square-wave jerks, and upbeat nystagmus. Thaker et al.[6] studied 17 mentally normal tobacco smokers and 11 nonsmokers. After tobacco smoking, the smokers had increased square-wave jerks but no change in their smooth pursuit scores. There were no significant oculomotor differences in the tobacco smokers who did not smoke at least 90 minutes before, compared to 11 nonsmokers. Smooth pursuit scores of the smokers after cigarette smoking were the same as the nonsmokers, presumably because there was less than one square-wave jerk per 0.5 Hz cycle in the smokers. Global smooth pursuit was scored on a 1 to 5 scale. Perhaps a more objective computer scoring technique would reveal a difference. Hence this study was undertaken to compare nonsmokers after sham smoking and smokers after cigarette smoking with use of an automated computer technique for scoring smooth pursuit. The method used also permitted simultaneous measurement of pupillary diameter. The results obtained are the subject of this report.

METHODS

This study was approved by the University of Michigan Medical Center Institutional Review Board for Approval of Research Involving Human Subjects.

Experimental design. Fourteen healthy adult tobacco smokers (mean ± SE age, 30.6 ± 2.6 years) and 20 adult nonsmokers (mean ± SE age, 31.5 ± 1.7 years) without any significant eye disease were recruited. They were of mixed racial backgrounds and varied in iris pigmentation from light blue to dark brown. Five of the 14 smokers and nine of the 20 nonsmokers were women. They smoked at least one-half pack but less than two packs of cigarettes per day for 1 or more years. The smokers were requested to abstain from smoking for at least 2 hours before the experiment. The subjects were allowed to smoke one of their preferred brand of cigarettes. The cigarettes ranged from 0.6 to 1.6 mg nicotine and 6 to 12 mg tar machine delivery. Volunteers were chosen and studied at random in response to oral and written notices and were paid $10 per hour for their time. They were briefly screened as healthy normal persons who denied substance abuse, including illicit drugs. Exclusion criteria included any psychiatric or medical illness that was not in remission, pregnancy, drinking more than four cups of coffee per day, and daily use of ethyl alcohol. However, urine testing was not done to confirm that the subjects were drug free at the time of the study. Performance was tested throughout the day, but preferably in the morning. Inasmuch as it was easier to recruit nonsmokers than smokers, the groups were of unequal size.

Smooth pursuit. According to the research protocol, eight separate measures were taken of each eye and the mean data of each were calculated for each group of volunteers before they started to sham or smoke. Smooth pursuit was measured at 5 minutes before and at 0, 3, 6, 10, 20, and 30 minutes after smoking a tobacco cigarette (smokers) or after sham smoking an unlit filter that looked like a real cigarette (nonsmokers). This protocol was used to determine the effects of tobacco smoking over a 30-minute interval after one cigarette was smoked. Smooth pursuit was determined objectively with a fixed menu-driven program with use of the EPS-100 Performance System Version 2.1 (Eye Dynamics Inc., Torrance, Calif.). This imaging system used a CCD video camera with NTSC synchronization. The field of view was 1.2 inches (horizontal) × 0.8 inches vertical ±5%. The measurement section used a viewport. A sampling frequency of 60 Hz with an accuracy ±10% was used for a 6.5 mm target. Measurement output included a video screen display on a 9-inch black-and-white monitor, as well as a printed hard copy. A light-emitting diode with a peak wavelength of 660 nm (green color) was set

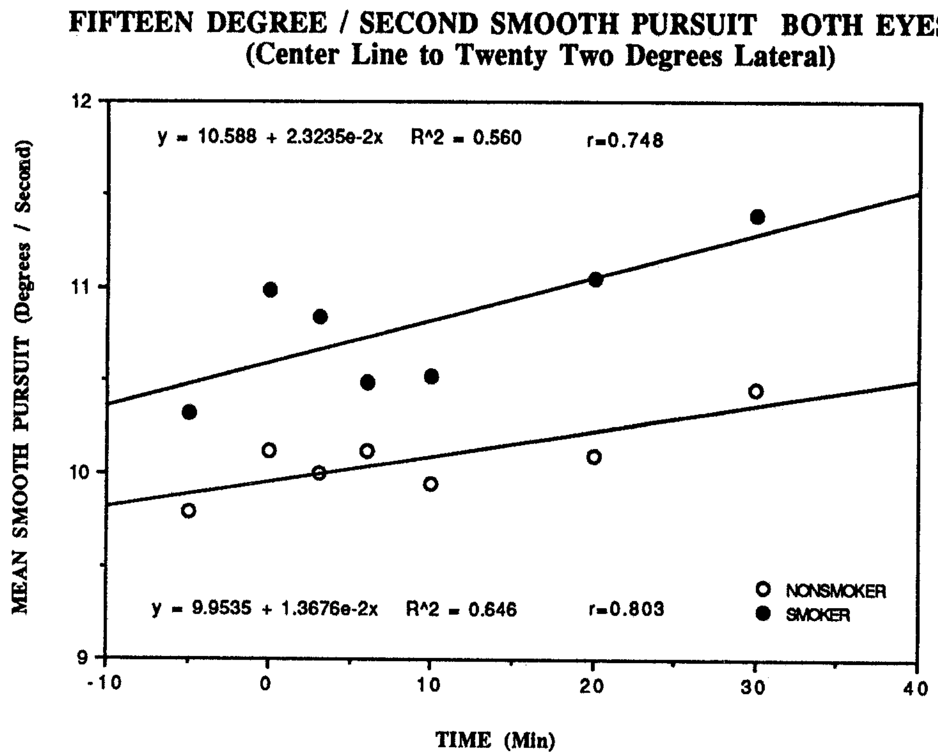

Fig. 1. Linear regression analysis of mean 15 degrees per second smooth pursuit with both eyes after sham smoking in nonsmokers and cigarette smoking in the smokers. Between −10 and 0 minutes, each group either sham smoked an unlit placebo cigarette or smoked a favorite cigarette. Both the nonsmokers and smokers tended to improve their smooth pursuit scores with repeated practice, but the improvement was greater in the smokers.

for dim (8 foot candles for 5 seconds) and bright (20 foot candles for 8 seconds) illumination. An infrared light-emitting diode with a peak wavelength of 920 nm provided direct illumination of the eye. The equipment configuration included a viewport, PC-compatible computer, video monitor, printer, and accessory cables. One video camera for each eye viewed the volunteer's eyes in total darkness when the face was flush with the viewport. The invisible infrared illumination allowed easy viewing of each eye with the infrared sensitive video camera. Each eye was video sampled 60 times per second for both eye position and pupil diameter. The data were stored in the computer. During each test, the subjects looked at and followed the target light-emitting diode, which provided a relatively small green spot at a nonretinal stimulation level. The target light changed from a dim to a bright spot with each eye tested during the programmed protocol. The equipment measured ocular smooth pursuit of each eye separately. The light target moved initially at 15 degrees per second (more rapid) from the center line to 44 degrees to the left, where it stopped for 2 seconds and moved back to the center line, then 44 degrees to the right, and then back. This sequence was repeated and, subsequently, at 35 to 44 degrees from the center line the target slowed to 6 degrees per second. Smooth pursuit was scored objectively by the criteria of the computer program and expressed as mean scores per second. Pupillary diameters were measured before, during, and at the end of each pursuit sequence with use of the same equipment as part of the fixed menu-driven program.

Statistical analysis. Smooth pursuit data were analyzed with use of one-way ANOVA with repeated measures (InStat 2.0, InStat for MacIntosh, 1993), as well as two-way ANOVA (BMDP Statistical Software, Inc., 1993), followed by the

Table I. Mean smooth pursuit of a target moving 15 degrees/second

	Both eyes		*Left eye*		*Right eye*	
Time (min)	*Nonsmokers*	*Smokers*	*Nonsmokers*	*Smokers*	*Nonsmokers*	*Smokers*
Before	9.79 ± 0.52	10.32 ± 0.62	8.27 ± 0.44	8.90 ± 0.65	8.88 ± 0.52	8.79 ± 0.62
0	10.13 ± 0.52*	10.99 ± 0.56	8.72 ± 0.56	10.07 ± 0.65**	9.02 ± 0.59	9.14 ± 0.56
3	10.00 ± 0.48	10.84 ± 0.62*	8.22 ± 0.49	9.36 ± 0.59	8.68 ± 0.58	9.02 ± 0.63
6	10.13 ± 0.55	10.49 ± 0.45	8.32 ± 0.56	9.36 ± 0.69	9.33 ± 0.58	9.02 ± 0.44
10	9.95 ± 0.61	10.52 ± 0.53	8.55 ± 0.56	9.19 ± 0.61	9.00 ± 0.63	9.26 ± 0.51
20	10.10 ± 0.57	11.05 ± 0.55*	8.60 ± 0.53	9.76 ± 0.56*	9.07 ± 0.58	9.31 ± 0.58
30	10.46 ± 0.43*	11.39 ± 0.58**	8.74 ± 0.41	10.24 ± 0.63**	9.68 ± 0.52*	9.50 ± 0.55*

Nonsmokers, $n = 20$; smokers, $n = 14$. All data are expressed as the mean per second ± SE. *$p < 0.05$; **$p < 0.01$ (correlated t test compared with before sham or cigarette smoking).

Table II. Mean smooth pursuit of a target moving 6 degrees per second

	Left eye		*Right eye*	
Time (min)	*Nonsmokers*	*Smokers*	*Nonsmokers*	*Smokers*
Before	2.50 ± 0.28	2.50 ± 0.40	2.35 ± 0.64	2.50 ± 0.51
0	3.50 ± 0.31**	3.29 ± 0.38*	2.90 ± 0.54	2.86 ± 0.52
3	2.95 ± 0.37	2.79 ± 0.53	3.00 ± 0.43	2.36 ± 0.58
6	2.80 ± 0.39	2.93 ± 0.53	3.60 ± 0.65*	3.07 ± 0.54
10	3.05 ± 0.39	2.79 ± 0.58	3.50 ± 0.48**	3.07 ± 0.60
20	2.90 ± 0.34	2.71 ± 0.54	2.80 ± 0.53	3.36 ± 0.64
30	2.79 ± 0.38	2.71 ± 0.50	3.60 ± 0.48*	3.14 ± 0.46*

Nonsmokers, $n = 20$; smokers, $n = 14$. All data are expressed as the mean per second ± SE. *$p < 0.05$; **$p < 0.01$ (correlated t test compared with before sham or cigarette smoking).

Tukey multiple-comparison procedure when a significant F ratio was obtained. An α level (p value) of 0.05 was used for all statistical tests. In this study, the subjects, selected from University of Michigan student and employee volunteers, were normally distributed. The measurements were based on a ratio scale because there was equal distance between scale points and real zero. Therefore the data were parametric. Because repeated measuring was used within factors, the Greenhouse-Geisser adjustment[7] was used in the calculation of p values. It met with assumption of sphericity.

RESULTS

Fifteen degrees per second smooth pursuit for both eyes (center line to 22 degrees lateral). One-way ANOVA repeated measures was conducted first. Each group of nonsmokers and smokers was independently analyzed as a function of time. Horizontal smooth pursuit scores for both eyes were significantly increased in the smokers [$F(6,97) = 3.33$; $p < 0.01$] but not in the nonsmokers [$F(6,139) = 1.41$; $p > 0.05$; Fig. 1]. The mean ± SE data for each group and each time before and after real or sham smoking are summarized in Table I. The mean ± SE presmoking baseline was 10.32 ± 0.62 degrees per second for the smokers and 9.79 ± 0.52 degrees per second for the nonsmokers. These differences were not statistically significant with use of a two-tailed independent Student t test ($t = 0.659$; $p > 0.05$; Fig. 1). The best nonsmoker performance was 30 minutes after sham smoking, with a mean ± SE of 10.46 ± 0.43 degrees per second. The smokers also performed best at 30 minutes after smoking a tobacco cigarette, with a mean ± SE of 11.39 ± 0.58 degrees per second. The overall data indicate that nonsmokers had a 7% improvement 30 minutes after sham smoking, presumably due to practice. On the other hand, the smokers had a 10% improvement, presumably due to smoking plus 30 minutes of practice.

A separate two-way ANOVA with repeated measures was also used. In this case, both the time after real or sham smoking, as well as differences between the two groups, were analyzed. To meet the assumption of homogeneity of variance (equal numbers of

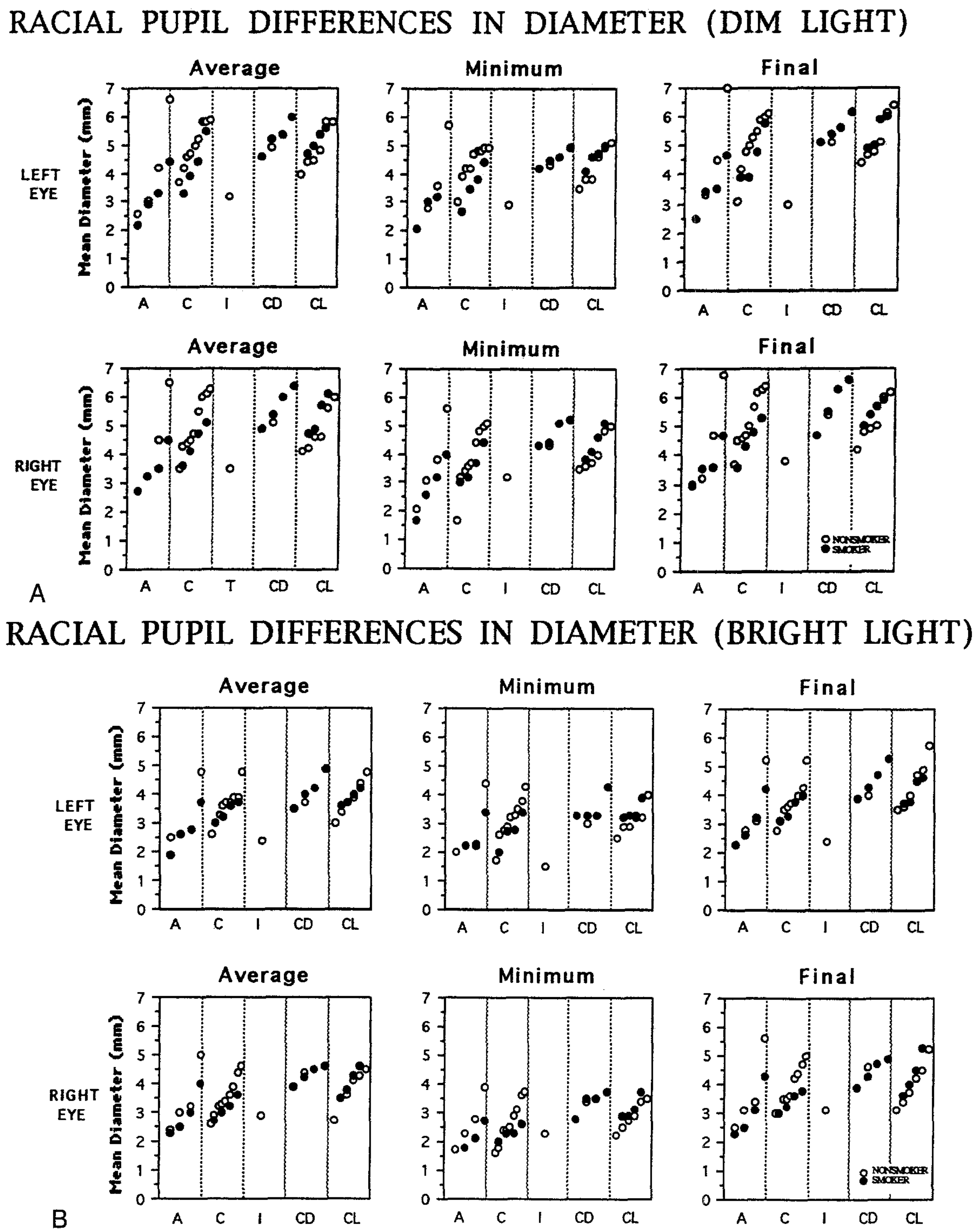

Fig. 2. Race-related differences in resting pupil diameter. The pupil diameter of each volunteer before sham or cigarette smoking is plotted as that person's average, minimum, or final diameter with dim (**A**) or bright (**B**) light. Nonsmokers *(open circles)* and smokers *(solid circles)* are illustrated. The one black nonsmoker who had a large resting pupil diameter was light skinned. The mean ± SE of each group for each condition is illustrated on the y-axis. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ (correlated Student *t* tests before and after sham or cigarette smoking). A, African American; C, Chinese; I, Indian; CD, Caucasian dark; CD, Caucasian light.

Table III. Mean ± SE pupil diameters (in millimeters)

	Black subjects (n = 8)	*White subjects (n = 10)*
Left eye		
Dim		
Minimum	2.81 ± 0.57	4.41 ± 0.18**
Average	3.65 ± 0.50	5.00 ± 0.20*
Final	3.93 ± 0.52	5.33 ± 0.22*
Bright		
Minimum	2.34 ± 0.44	3.24 ± 0.14*
Average	2.96 ± 0.32	3.87 ± 0.16*
Final	3.21 ± 0.36	4.30 ± 0.22*
Right eye		
Dim		
Minimum	3.26 ± 0.43	4.22 ± 0.19*
Average	3.85 ± 0.45	5.05 ± 0.23*
Final	4.05 ± 0.46	5.31 ± 0.20*
Bright		
Minimum	2.16 ± 0.40	2.98 ± 0.15
Average	3.18 ± 0.32	3.89 ± 0.19
Final	3.35 ± 0.39	4.15 ± 0.23

$^*p < 0.05$, $^{**}p < 0.01$ (group comparison Student t test).

subjects in each group, $n = 14$), the nonsmokers were matched as closely as possible by means of gender, race, and age to the smokers. The remaining six nonsmokers were deleted from this analysis. The main effect was that both smokers and nonsmokers performed better over time on horizontal ocular fast pursuit [$F(6,156) = 3.63$; Greenhouse-Geisser adjusted[7]; $p < 0.0001$]. In other words, both groups improved with repeated tests as a function of learning. However, with this analysis no significant differences exist between the nonsmoker group and the smoker group [$F(1,156) = 0.97$; $p > 0.05$], as well as no significant interactions [$F(6,156) = 1.34$, $p > 0.05$].

Fifteen degree per second smooth pursuit for each eye (center line to 22 degrees, and 22 to 47 degrees). The data for each eye from midline to 22 degrees and from 22 to 47 degrees were independently subjected to both one- and two-way ANOVA with repeated measures. Each group of nonsmokers and smokers was analyzed as a function of time. Smooth eye pursuit for only the left eye, the first and second time from the center line to 22 degrees lateral, was significant with use of one-way ANOVA [$F(6,97) = 2.58$; $p < 0.05$, and $F(6,97) = 2.84$; $p < 0.05$, respectively). No significant change in smooth pursuit for the right eye for the tobacco smokers was obtained. The nonsmokers showed no significant change for smooth pursuit for either eye.

Six degree per second smooth pursuit for each eye (22 to 47 degrees). There were no significant differences among nonsmokers and smokers with use of separate one-way ANOVA with repeated measures over time. However, with use of correlated t tests, both groups showed some improvement over control, nonsmokers more frequently than smokers (Table II).

Racial-related differences in pupil diameter. There was large variability in basal pupillary diameter (average, minimum, and final) within both groups of nonsmokers and tobacco smokers. This was surprising because the environmental conditions were rigidly controlled and identical for each volunteer. During the study, it was noted that black subjects had relatively constricted pupils compared with white subjects. The present data from 34 adult men and women are plotted in Fig. 2 in relationship to race-related origins for the average, minimum, and final pupil diameters for dim and bright light for both groups before sham or tobacco smoking. No obvious distinction in pupil size was observed between smokers and nonsmokers in the presmoking or presham smoking period. Subjects with both darkly pigmented irises and skin had more-constricted pupils. The mean ± SE pupil diameters of the black subjects and white subjects with light irises under dim and bright light are given in Table III. The differences are statistically significant, as noted.

Effects of sham and tobacco smoking on pupil diameter to dim light. The mean ± SE data of both groups for both eyes are plotted in Fig. 3 as bar graphs before and at various times after real or sham smoking. The baseline (−5 minutes) diameter of the left and right pupils was similar, with a mean about 4.6 mm in the nonsmokers. Surprisingly, the mean control (−5 minutes) diameter of the left pupil of the smokers was slightly smaller (about 4.4 mm) than the mean right pupil diameter (4.55 mm). After sham smoking, the nonsmokers tended to have significantly greater mydriasis in their left pupils compared with their right pupils, which dilated slightly less. Statistically significant differences from baseline are noted by the asterisks (*) with $p < 0.05$. In contrast to the nonsmokers after sham smoking, the smokers did not have any significant pupillary dilatation in either eye after they smoked a cigarette. However, at each time point their left pupils were more constricted than their right pupils.

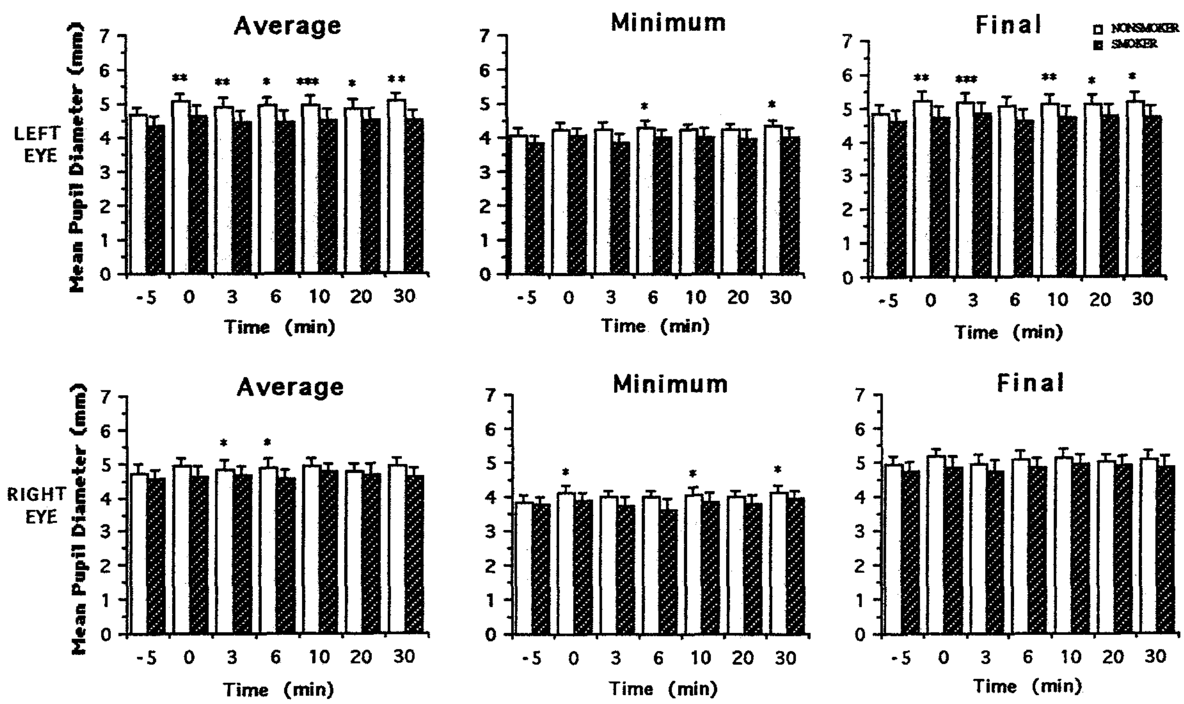

Fig. 3. Effects of sham and cigarette smoking on mean pupil diameter with dim light in nonsmokers and smokers during repeated smooth pursuit testing. The height of the bars represent the average, minimum, and final pupil diameter for each eye under dim light (8 foot candles) for 5 seconds. Note that the most significant differences in pupil diameter between nonsmokers and smokers are in the left eye. $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ (correlated Student t test before and after sham or cigarette smoking).

Effects of sham and tobacco smoking on pupil diameter to bright light. The mean ± SE data of both groups for both eyes are plotted in Fig. 4. The baseline (−5 minutes) mean pupil diameter of the left and right eyes of both nonsmokers and smokers was similar. The nonsmokers after sham smoking tended to have a slight increase in mean pupil diameter that was more significant in the left than the right eye. In contrast, the tobacco smokers after cigarette smoking did not show any mydriasis. There was a tendency for a slight left eye miosis at the 6- and 20-minute times that was not statistically significant.

Relationship of baseline pupil diameter to sham and tobacco smoking. The median baseline pupil diameter in dim light for the 14 tobacco smokers was 4.4 mm. Hence the smokers were divided into two subgroups below and above the median pupil size. The subgroup of tobacco smokers with pupil diameters below 4.4 mm had less of a tendency to dilate after smoking, whereas the subgroup of tobacco smokers above 4.4 mm tended to dilate. In the nonsmokers, the baseline median pupil diameter was 4.7 mm. However, after sham smoking the subgroup below and above the median showed clear differences in the same direction, in contrast to the tobacco smokers.

Cardiovascular responses of sham and cigarette smoking. The mean ± SE data on heart rate and systolic and diastolic blood pressure before and after sham or cigarette smoking to each group are illustrated in Fig. 5. Nonsmokers after sham smoking had a significant decrease in heart rate but no change in blood pressure. In contrast, the smokers after smoking a cigarette had small but statistically significant increases in heart rate and systolic and diastolic blood pressure.

DISCUSSION

Neveling and Kruse[8] observed clinically that tobacco smoking induced nicotine nystagmus. A total of 70 normal subjects were studied before and after smoking. Twenty-six had upbeat, 11 had horizontal, and four had oblique vertical nystagmus after smok-

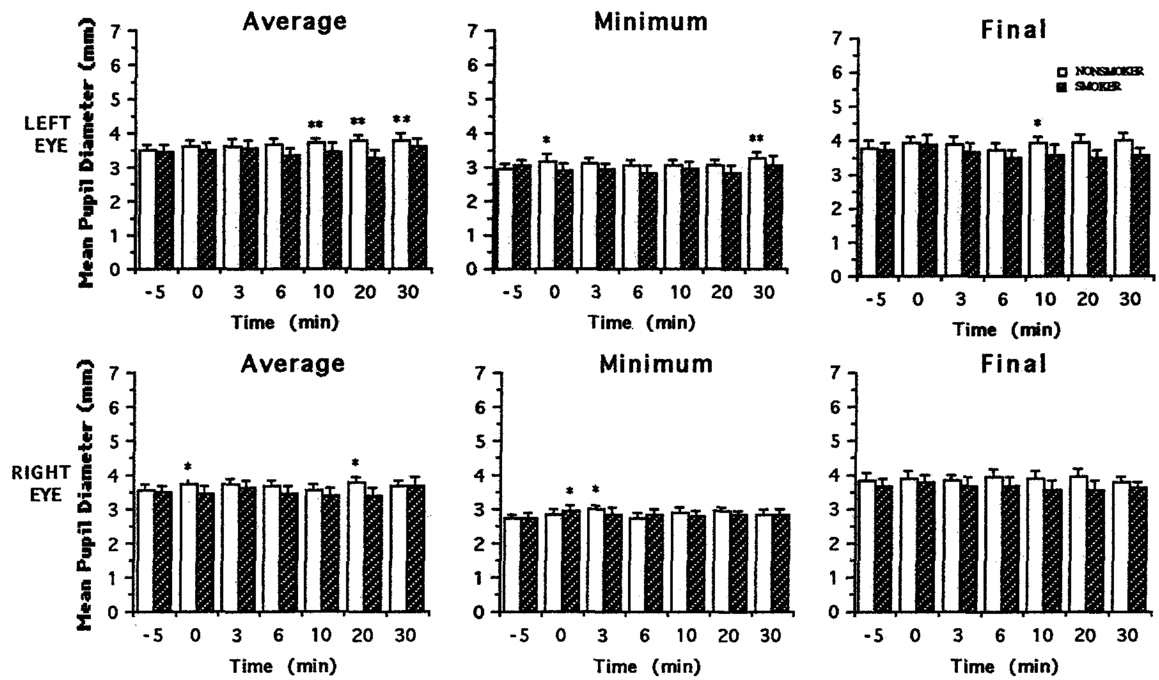

Fig. 4. Effects of sham and cigarette smoking on mean pupil diameter with bright light in nonsmokers and smokers. The data are plotted similar to Fig. 3. The bright light was 20 foot candles for 8 seconds. $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ (correlated Student *t* test before and after cigarette smoking).

ing. Subsequently, Sibony et al.[9] used quantitative eye movement recordings to study this phenomenon in four healthy subjects, two of whom were nonsmokers. All four had normal visual acuities and absence of nystagmus. Primary position upbeat nystagmus developed in each volunteer in total darkness with their eyes open. The nystagmus was also observable in a room with normal light if the subject wore +30.00 (diopter) lenses. Visual fixation on a stationary target (light on) caused a dramatic suppression of both the horizontal and vertical eye movements of tobacco-induced upbeat nystagmus.[5,9] These authors pointed out that the latter could result from a disturbance of the peripheral vestibular system, the central neuronal integrator, or the central smooth eye pursuit system. After tobacco smoking, body sway increases when a smoker's eyes are closed. The enhanced body sway is suppressed by periodic saccadic eye movements when the eyes follow a visual target.[10] In all probability, a similar mechanism is involved within the central nervous system for nicotine-induced nystagmus that spares visual-vestibular pathways. Uchida et al.[10] also noted that closing the eyes before smoking caused large, slow eye movements, which were accompanied by EEG alpha waves recorded from the occipital-parietal areas. After subjects smoked, the EEG was more desynchronized to eye closing and the large, slow repetitive eye movements were replaced with small, rapid repetitive eye movements. The authors suggested these two phenomena were due to increased arousal.

Klein and Andresen[11] studied an equal number (13) of patients with schizophrenia and mentally normal control smokers who were abstinent for 2 hours before and immediately after smoking one and then another cigarette. Smooth pursuit eye movement saccades of large amplitude were reduced after smoking. These authors concluded that suppression of large amplitude saccades was due to increased attention, as also described by Holzman et al.[12] The patients with schizophrenia showed a less prominent reduction than the normal control subjects, perhaps because the former were much heavier smokers and therefore may have been more tolerant to nicotine.

Tibbling and Henriksson[13] studied 21 healthy smokers who were abstinent from tobacco for 2

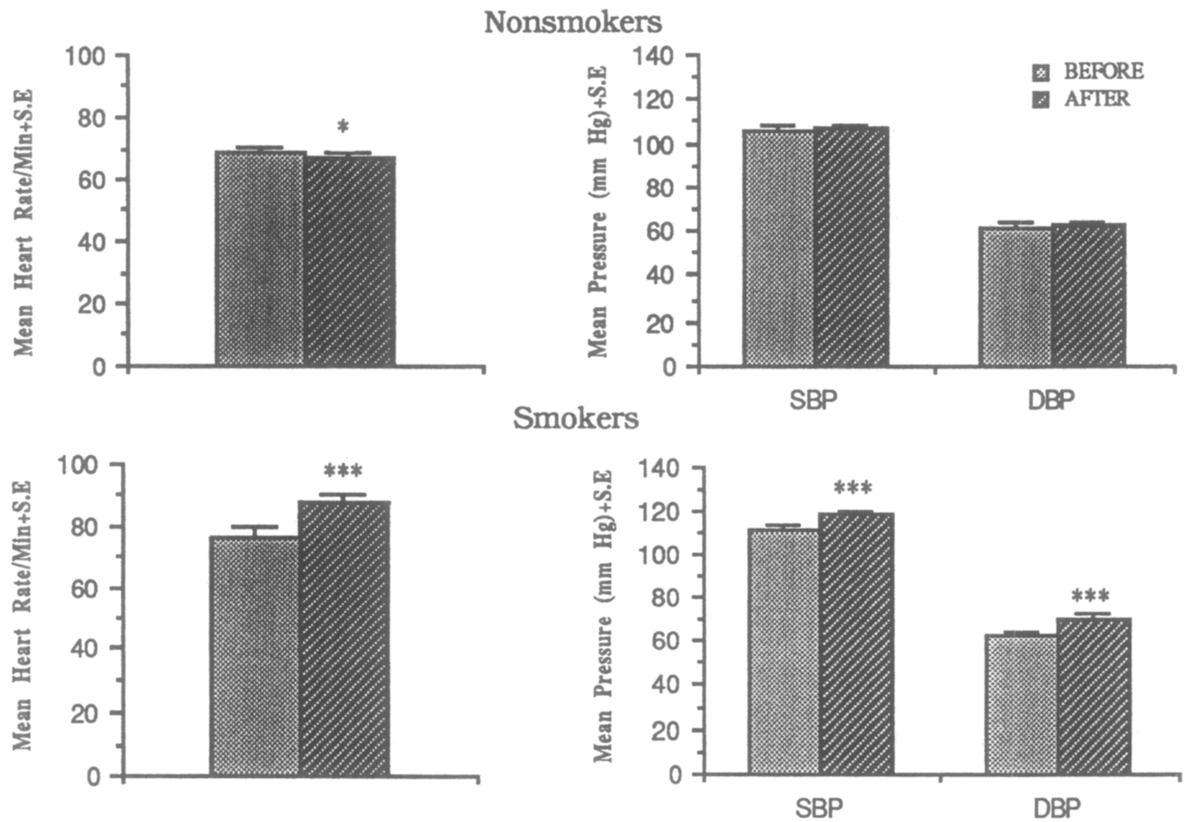

Fig. 5. Effects of sham and cigarette smoking on mean heart rate and systolic and diastolic blood pressure in nonsmokers and smokers. Each cardiovascular parameter was measured 5 minutes before and after sham or cigarette smoking and the mean data ± SE are illustrated. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ (correlated Student t test before and after cigarette smoking).

hours before and immediately after smoking a cigarette. The test subjects sat in the dark with their eyes open watching a rotating device that could be accelerated to 120 degrees per second for 1.8 seconds. Horizontal eye movements in a clockwise rotation in the dark dramatically decreased in amplitude and increased in frequency after smoking. The speed of the fast component of nystagmus markedly decreased, whereas the speed of the slow component and eye deviation in the direction of the fast component were not affected. The authors noted that a decrease in the velocity of the fast component tended to lower instead of increase its frequency. Therefore the more frequent interruption of the slow by the fast component accounted for the change observed, presumably by an action of tobacco smoke within the brain.

Thaker et al.[6] found that tobacco smoking increases square-wave jerks during pursuit eye movements in 22 normal volunteers, of which 17 were smokers and five nonsmokers. All other eye movements in both smokers and nonsmokers, including a smooth pursuit eye movement score to a spot of light moving in the dark at 0.5 Hz, were unaffected by smoking first one and then a second 1.43 mg nicotine commercial cigarette midway through the testing procedure. The smokers had a mean ± SE of 0.50 ± 0.31 square-wave jerks per cycle before and 0.69 ± 0.4 after smoking ($p < 0.018$). The nonsmokers (who were able to smoke) had a mean ± SE of 0.54 ± 0.35 square-wave jerks per cycle before and 0.88 ± 0.89 after smoking. There were significant order times smoking condition interactions ($p < 0.023$), and a significant effect of smoking ($p < 0.023$).

The significance of square-wave jerks, as well as their precise definition, has been discussed by Herishanu and Sharpe[14] and Elidan et al.[15] Although most investigators consider square-wave jerks with the eyes open to be pathologic, Herishanu and Sharpe[14] and Elidan et al.[15] point out that square-wave jerks can be sporadic and nonspecific in normal subjects. That the ocular jerks occur especially in the dark or with the eyelids closed, and are suppressed by visual fixation, indicates that afferent visual input is important to reduce them. Perhaps as Tibbling and Henriksson[13] have shown, an increase in their frequency and a decrease in amplitude is an index of a person's state of arousal. The key practical issue is whether the nicotine-induced nystagmus, which Neveling and Krause[8] describe as occurring with tobacco smoking, affects visual tracking or other visually related task performance.

Friedman and Meares[16] reported that tobacco smoking increases the amplitude of evoked potential components V-VI and VI-VII in the visual system and decreases component N_2P_2 in the auditory system. They suggest that tobacco smoking enhances visual input. They point out that such an interpretation reconciles several disparate behavioral findings. Warwick and Eysenck[17] and Tong et al.[18] reported that smoking improves visual discrimination task performance. However, smoking reduces meaningless noise, as reflected in the rate of habituation,[19] or noise distraction on reaction time.[20] Tarriere and Hartemann[21] reported that after smoking tobacco, smokers have enhanced vigilance for visual cues. Tong et al.[22] found that smoking lowers vigilance for auditory cues. Two additional control groups should be studied in the future on smooth pursuit performance: tobacco smokers without nicotine and nonsmokers with nicotine. The present study indicates that, immediately after smoking a cigarette, tobacco smokers have a slight advantage over nonsmokers in this visual task.

This study differs in important respects from others previously reported on the effects of nicotine or tobacco smoking on pupil diameter. The imaging system used was specifically designed to obtain objective measures of both pupil diameter and ocular smooth pursuit performance in subjects screened for potential substance abuse. All of the subjects were probably motivated to improve their smooth pursuit performance and, hence, the pupillary changes observed are confounded with the issues of (1) repeated testing which facilitated learning and (2) sham versus cigarette smoking. The pupillary data obtained in the present study indicate that the usual nonsmoker response to repeated smooth pursuit testing of slight pupillary dilatation is not present in tobacco smokers. Perhaps the tobacco smokers are less apprehensive or perhaps smoking causes the expected pupillary constriction and performance-induced dilatation to algebraically cancel each other.

Even with a limited number of 34 subjects, it is clear that there are significant race-related differences in baseline pupil diameter. The present study confirms the observations of Obianwu and Rand[23] that men with dark brown irises and skin pigment tend to have smaller pupils than men with light colored irises and skin. There have been many reports that persons with dark brown irises do not show as much mydriasis to sympathomimetic eyedrops as do persons with light colored irises. Obianwu and Rand, using ephedrine, also confirmed the early observations of Chen and Poth.[24] The present study indicates that before tobacco smoking (after at least a 2-hour abstinence), there is no difference in pupil diameter between nonsmokers and smokers.

Inasmuch as pupil diameter was not measured during the actual smoking period, this study cannot contribute directly to the issue of pupil diameter during smoking. After a cigarette was smoked, there was no increase in mean pupil diameter in the smokers, in contrast to the nonsmokers sham smoking. This is consistent with reports that slight miosis occurs shortly after nicotine intake or tobacco smoking.[25-29] In the present study this was observed as preventing the usual pupillary dilatation seen in nonsmokers engaged in a repeated smooth pursuit task. The greater effect on the left than the right pupil after tobacco smoking is consistent with data that the two brain hemispheres respond somewhat differently to nicotine.[30] It is possible that nicotine affects the dominant more than the nondominant eye. In the present study, this parameter was not measured. In retrospect, it should have been.

It is clear that nicotine intake or tobacco smoking has far greater sympathomimetic effects on the cardiovascular system than on the pupil. The subtle sympathomimetic effects of nicotine or tobacco smoke during actual smoking on the pupil reported in the literature are small and very transient and were not studied.[25-29] In the present study, the parasympathetic effects on the pupil last for at least 30 minutes beyond the period of tobacco smoke inhalation.

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