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Sensory and physiologic effects of menthol and nonmenthol cigarettes with differing nicotine delivery

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Abstract

Many smokers choose menthol-flavored cigarettes, however, the influence of menthol on the effects of smoke-delivered nicotine is unknown. Research and commercial cigarettes, menthol and nonmenthol, that delivered a wide range of nicotine were evaluated. Menthol ($n = 18$) and nonmenthol ($n = 18$) cigarette smokers participated in a single session during which three cigarettes were smoked 45 min apart, in random order. Federal Trade Commission (FTC) nicotine yields of the three cigarettes were: research, low yield, 0.2 mg, commercial cigarettes (average), 1.2 mg; research, high yield, 2.5 mg. Commercial and high-yield cigarettes increased heart rate (HR) and blood pressure more than low-yield cigarettes; although, no differences in exhaled carbon monoxide (CO) occurred. Participants smoked commercial cigarettes faster and with fewer puffs than either of the research cigarette indicating production differences can affect topography. There was a significant group by cigarette interaction on satisfaction, and relief from cigarette craving. High-yield nonmenthol cigarettes reduced craving and were rated as more satisfying than high-yield menthol cigarettes. No differences between menthol and nonmenthol cigarettes on other subjective measures (strength, psychological reward, negative effects) were observed. Our findings indicate that nicotine delivery, but not mentholation, influences cardiovascular and most subjective measures. These results illustrate the importance of threshold levels of nicotine on subjective responses to cigarette smoking.

Keywords: Placebo cigarettes; Menthol; Denicotinized; Smoking; African Americans

1. Introduction

Smoking is a complex behavior that involves the delivery of nicotine, a pharmacologically active substance, and as many as 4000 other compounds and constituents of tobacco smoke (U.S. Department of Health and Human Services, 1988). Although the reinforcing and discriminative stimulus effects of cigarettes depend upon the occupation by smoke-delivered nicotine of specific brain acetylcholine receptors (Rose et al., 2000; Stolerman et al., 1987), the role of the other compounds in cigarette smoke is unknown. Additionally, sensory cues evoked by the heat and feel of smoke, the sight and smell of the burning cigarette rod and the behavior of lighting, holding and inhaling a cigarette appear to be involved in the effects of cigarette smoking (Pritchard et al., 1996; Robinson et al., 2000). Cigarettes that contain and deliver components of tobacco smoke at and various levels of nicotine could be used to distinguish the nicotine-induced effects from those engendered by the behavior of smoking (Robinson et al., 2000). In fact, several research studies have demonstrated that cigarettes that contain and deliver little or no nicotine decrease desire to smoke, cigarette craving and other subjective signs of tobacco withdrawal (Gross et al., 1997; Pickworth et al., 1999; Robinson et al., 2000).

Although nearly 25% of Caucasian smokers and 70–80% of African American smokers in the United States choose menthol-flavored cigarettes (Cummings et al., 1987; Orleans et al., 1989; Sidney et al., 1979), the effect of mentholation on sensory and physiologic effects of cigarettes has not been systematically studied. Recently, Pritchard et al. (1999) reported that denicotinized menthol cigarettes had no effect on EEG, cardiovascular and subjective responses. Those data suggested that menthol flavoring itself had no physiologic effects, however, the effects of mentholation on cigarettes that deliver different amounts of nicotine have not been studied. In cooperation with the National Institute on

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Drug Abuse, Murty Pharmaceutical (Lexington, KY) recently developed four new research cigarettes (menthol and nonmenthol) that deliver very high and very low levels of nicotine. In the present study, the interaction of menthol and nicotine delivery of these new research cigarettes and commercial cigarettes on cardiovascular effects, smoke delivery factors and cigarette taste and satisfaction were assessed. This study was designed to independently determine how nicotine and menthol interact to influence the physiologic and subjective effects of smoking and to assess the acceptability of these new cigarettes for tobacco research. To control for novelty effects of smoking cigarettes of differing flavor, a group design was chosen. Subjects that ordinarily smoked menthol cigarettes received menthol cigarettes in the experiment and nonmenthol smokers received nonmenthol cigarettes.

2. Methods

2.1. Subjects

Thirty-six (36) research volunteers participated in the study. Subjects were selected based on good health and a smoking history of at least 2 years, smoking 15 or more cigarettes per day. Prior to their participation, subjects signed an informed consent document that had been approved by the local Institutional Review Board and met U.S. Department of Health and Human Services guidelines for the protection of human research participants. They were paid US$60 for their participation.

Subjects were assigned to two groups (18 subjects each) based on the characteristics of their usual cigarette — menthol or nonmenthol. The menthol group was composed of 13 men and 5 women; 17 were African American, 1 was Caucasian. The nonmenthol group was composed of 14 men and 4 women; 3 were African American, 15 were Caucasian. The groups did not significantly differ as a function of gender; they differed significantly by ethnic composition (Pearson $\chi^2 = 22.1$, $P < .001$) The groups were similar for age (mean = 32.6 years), weight (75.4 kg), nicotine dependence, Fagerström (Heatherton et al., 1991) score = 5.8, cigarettes per day = 23.1 and years smoked = 15.9. The nicotine yield as determined by the methods (Federal Register, 1967; Pillsbury, 1996) of the Federal Trade Commission (FTC) of their usual brands of cigarettes differed between groups. The FTC nicotine yield of the brands smoked by the menthol group averaged 1.26 mg, whereas the FTC nicotine yield of the brands in the nonmenthol group averaged 1.02 mg [$F(1,34) = 18.95$, $P < .001$].

2.2. Experimental cigarettes

Four research (Murty Pharmaceutical) cigarettes were made (FTC yield: nicotine mg, tar mg, puffs/cigarette): nonmenthol, high yield (2.5, 20.9, 12.2); menthol, high yield (2.5, 20.8, 12.6); nonmenthol, low yield (0.2, 12.4, 8.3); and menthol, low yield (0.2, 11.2, 8.3). Nicotine was removed from the tobacco of the low-yield cigarettes by supercritical fluid extraction techniques. The research cigarettes were all 85 mm in length (king size) and filtered with cellulose acetate filters and commercially available citrate paper. The pressure drop for the research cigarettes ranged from 11.2 to 13.8 cm water. The commercial cigarettes (FTC yield: nicotine mg, tar mg, puffs/cigarette) were: Newport (1.3, 17, 10.9), Kool (1.1, 16, 8.2), Winston (1.1, 16, 10.9) and Marlboro (1.1,16. 11.9).

On the study day, the cigarettes were dispensed from the pharmacy in vials labeled as Cigarettes 1, 2 and 3. A band of white opaque tape was wrapped around the tobacco rods of all cigarettes to obscure the trademarks of the commercial cigarettes. Subjects smoked 50 mm of the tobacco rod to the edge of the tape.

2.3. Dependent measures

Before and after smoking each cigarette, systolic (SBP) and diastolic (DBP) blood pressure (seated) and heart rate (HR) were measured using an automated cardiovascular monitor (Datascope, Paramus, NJ). Before and after smoking exhaled carbon monoxide (CO) was measured in parts per million (ppm) with a CO sensor (Vitalograph, Lenexa, KS). Time to smoke the cigarette to a defined length (50 mm of tobacco rod) and the number of puffs were recorded. After each cigarette, subjects completed a Duke Sensory Questionnaire (Behm and Rose, 1994) and a Cigarette Evaluation Scale (Westman et al., 1992). The Duke Sensory Questionnaire has nine items: (1) How much did you like the puffs? (2) How satisfying were the puffs? (3) How high in nicotine were the puffs? (4) How similar to your own brand (cigarette) were the puffs and rate the strength of the puffs on (5) tongue, (6) nose, (7) back of mouth and throat, (8) windpipe and (9) chest? All questions were answered on a scale of 1 to 7, anchored at the extremes with *not at all* and *extremely*. To avoid multiple comparisons and to distinguish the effects of nicotine from menthol on measures of "strength" responses to Questions 5–9 were summed. The Cigarette Evaluation Scale is an 11-item questionnaire that evaluates the cigarette for: (1) satisfying; (2) tastes good; (3) makes you dizzy; (4) calms you down; (5) makes you concentrate; (6) feels more awake; (7) reduces hunger for food; (8) makes you nauseous; (9) feels less irritable; (10) did you enjoy the sensations of the smoke in your throat and chest; and (11) did it immediately reduce your craving for cigarettes. These questions were answered on a 1 to 7 scale as described above. For data analyses, Question 1 (Satisfaction) and Question 11 (Craving Relief) were analyzed alone, and Questions 2 and 10 (Peripheral Sensation), Questions 4, 5, 6, 7 and 9 (Psychological Reward) and Questions 3 and 8 (Negative Effect) were summed (Rose et al., 2000).

2.4. Procedure

This double-blind study was performed on an outpatient basis at NIDA, Intramural Research Program. Subjects were assigned to the two groups on the basis of their usual flavor of cigarettes (menthol or nonmenthol). This assignment was chosen to decrease the influence of novelty of cigarette flavor on the subjective evaluations of the cigarettes. Subjects participated in a single experimental session where they smoked three cigarettes separated by 45 min. Subjects were not required to be tobacco abstinent on the study day. The first cigarette of the experimental session was smoked about 45 min after the subject had smoked their last cigarette before reporting to the lab. The presentation of cigarettes was determined by a Latin-square design. Each subject smoked a research low- and high-yield cigarette and a commercial cigarette. Subjects who ordinarily smoked menthol cigarettes smoked only menthol cigarettes in the experimental session; whereas subjects that ordinarily smoked nonmenthol cigarettes smoked nonmenthol cigarettes in the experiment. However, the commercial cigarette was never the usual brand that the subject smoked.

2.5. Data analyses

Repeated-measures analysis of variance (ANOVA) was used to compare continuously distributed variables with between- and within-subjects factors (Winer et al., 1991). The between-subjects factor had two levels: menthol and nonmenthol cigarette; the within-subjects factors had three levels: commercial cigarette, research high and low nicotine yield. Significance was evaluated using the Greenhouse–Geisser epsilon adjustment. Post hoc comparisons between cigarettes were performed by adjusting P values to the number of comparisons (Bonferroni's method). Categorical data were compared by the chi-square test. Differences were considered significant at $P < .05$. Data are presented as means ± S.D. unless otherwise indicated. Data were analyzed using SPSS statistical software (Version 10; SPSS, Chicago IL).

3. Results

3.1. Physiologic measures

Commercial and high-yield cigarettes increased HR more than the reduced-yield cigarettes (Fig. 1). There was a significant effect of cigarette [$F(2,68) = 6.92$; $P < .01$] but no main effect of group (menthol vs. nonmenthol) and no significant group by cigarette interaction. Post hoc tests indicated that HR increase after smoking commercial and high-yield research cigarettes differed significantly from the low-yield cigarettes, but not from each other.

Commercial and high-yield research cigarettes increased SBP by 4.1 and 2.2 mm Hg; but low-yield nicotine cigarettes decreased SBP by 0.6 mm Hg. The analyses indicated a significant effect of cigarette [$F(2,68) = 4.3$; $P < .02$] but no significant main effect of group and no significant group by cigarette interaction. Post hoc tests indicated that SBP did not differ after the high-nicotine-yield research and commercial cigarettes. The SBP response to the low-yield research cigarettes differed significantly from the other cigarettes.

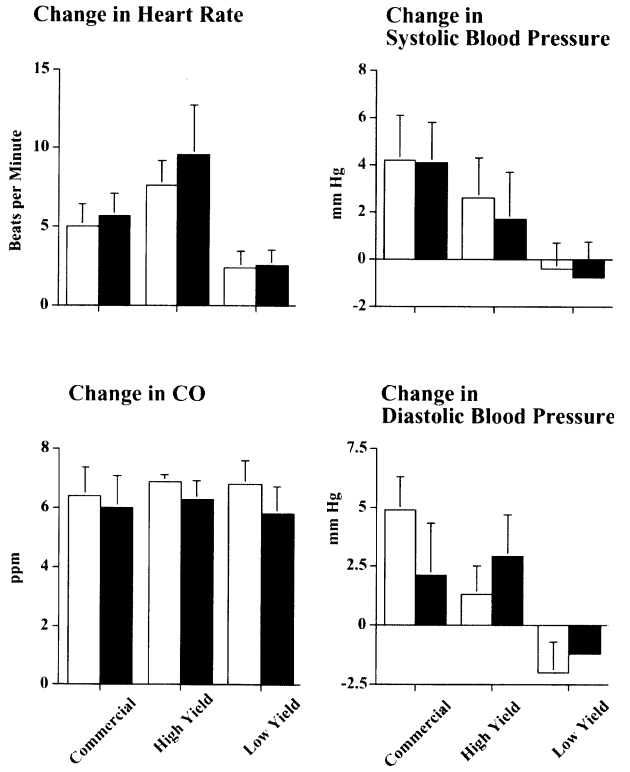

Fig. 1. Average differences between pre- and postsmoking HR, blood pressures and CO for menthol (open bars, $n = 18$) and nonmenthol (closed bars, $n = 18$) cigarettes. All cigarettes for the menthol group were menthol; and nonmenthol for the other group. Commercial cigarettes were not the usual brand that the subjects smoked. Research cigarettes were low yield (0.2 mg nicotine) and high yield (2.5 mg).

The commercial and high-nicotine-yield research cigarettes caused a small but significant increase in DBP. DBP increased by 3.5 and 2.1 mm Hg after commercial and high-nicotine-yield cigarettes, respectively. DBP decreased by 1.5 mm Hg after the low-yield research cigarette. The analyses indicated a significant effect of cigarette [$F(2,68) = 5.8$; $P < .01$] but no significant main effect of group and no significant group by cigarette interaction. Post hoc tests indicated that DBP increased significantly more after smoking the commercial and high-yield research cigarettes than the low-yield cigarette.

Changes in exhaled CO are illustrated in Fig. 1. All cigarettes increased exhaled CO by amounts that did not significantly differ as a function of the cigarette type or mentholation. There was no significant interaction between cigarette type and group.

3.2. Smoking variables

The number of puffs to smoke the 50 mm tobacco rod is illustrated in the upper panel (Fig. 2). The average number of puffs was 8.4, 11.9 and 12.8 for the commercial, high-yield and low-yield cigarettes, respectively. The analyses indicated a significant difference between cigarettes [$F(2,68) = 53.7$, $P < .01$]. Post hoc analyses confirmed that significantly fewer puffs were taken to smoke the commercial cigarette than either of the research cigarettes. The mean number of puffs to smoke the high-yield and the low-yield research cigarettes did not significantly differ.

Time to smoke the cigarettes is illustrated in the lower panel of Fig. 2. Time to smoke the commercial cigarettes averaged 284.4 s, whereas the time to smoke the high- and low-yield research cigarettes averaged 426.6 and 407.1 s, respectively. The analyses indicated there was a significant effect of cigarette [$F(2,68) = 49.8$; $P < .01$] and a significant cigarette by group interaction [$F(2,68) = 3.9$; $P < .05$]. There was no significant main effect of group. Post hoc tests indicated that the average time to smoke the commercial cigarette was significantly less than the times to smoke either the high- or the low-yield research cigarettes. Because 17 of the 18 subjects in the menthol group were African American, the analyses were also run using ethnicity as the between-subjects factor. This analysis indicated no significant effect of ethnic group.

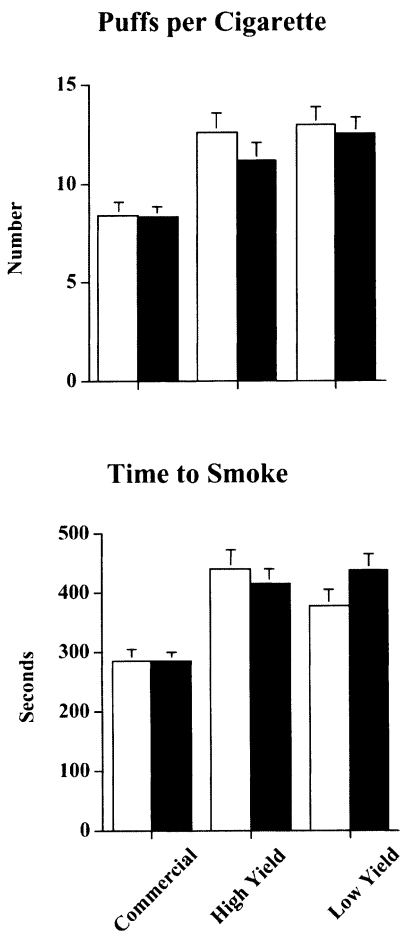

Fig. 2. Average puffs per cigarette and time to smoke for menthol (open bars, $n = 18$) and nonmenthol (closed bars, $n = 18$) cigarettes. Cigarette and group description are given in Fig. 1.

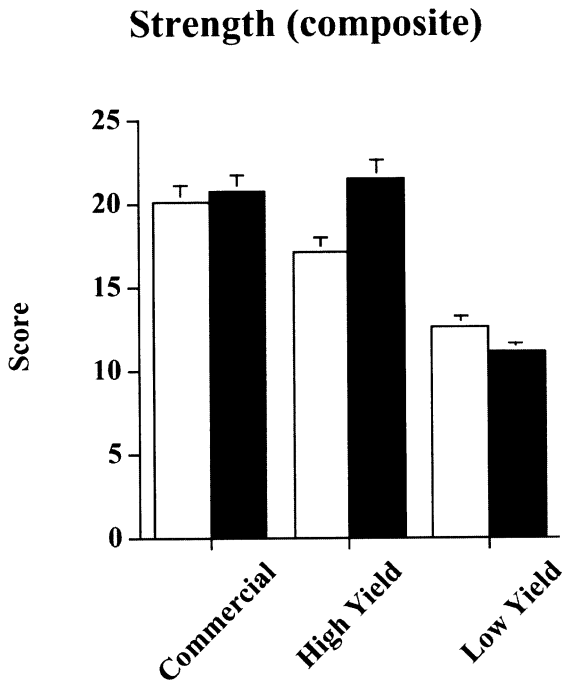

Fig. 3. Average overall rating of strength at nose, tongue, throat, wind pipe and lung (total possible score = 35) for menthol (open bars, $n = 18$) and nonmenthol (closed bars, $n = 18$) cigarettes. Cigarette and group description are given in Fig. 1.

3.3. Subjective measures

Data from the Duke Sensory Questionnaire (Behm and Rose, 1994) are illustrated in Fig. 3 and the top half of Table 1. As shown in Table 1, there was no main effect of group (menthol vs. nonmenthol) and no significant interaction between group and cigarette. However, there was a significant main effect of cigarettes on questions of like puffs, satisfaction with puffs, high in nicotine and similar to own brand. In general, participants preferred commercial and high-yield research cigarettes (cigarettes C and H) to low-yield research cigarette (cigarette L). Compared to their own brand the commercial cigarette was rated as significantly more similar than either of the research cigarettes.

Fig. 3 illustrates the perceived strength of the cigarettes in five areas of the respiratory tract: nose, tongue, mouth, windpipe and lung. The ANOVA indicated that there was a main effect of cigarettes [$F(2,68) = 15.6$; $P < .01$] but no significant main effect of group and no significant group by cigarette interaction. Post hoc pairwise comparisons showed that the commercial and high-yield research cigarettes were rated significantly stronger than the low-yield research cigarette.

Table 1
Subjective responses to commercial, research high- and low-yield cigarettes

	Main effect of group (menthol vs. nonmenthol)	Group × cigarette interaction	Main effect of cigarette	Pairwise comparisons
Duke Sensory Questionnaire				
Like puffs	0.6; ns	3.0; ns	6.1; $P<.01$	C > L; H = L; C = H
Puff satisfaction	0.7; ns	2.4; ns	11.9; $P<.01$	C > L; H > L; C = H
High in nicotine	0.6; ns	2.3; ns	11.2; $P<.01$	C > L; H > L; C = H
Similar to own	0.8; ns	0.3; ns	13.5; $P<.01$	C > H; C > L; H = L
Cigarette Evaluation Scale				
Satisfaction	0.7; ns	3.1; $P<.05$	14.9; $P<.01$	C > L; H > L; C = H
Craving Relief	0.6; ns	4.8; $P<.02$	11.6; $P<.01$	C > L; H > L; C = H
Peripheral Sensation	0.1; ns	2.0; ns	6.4; $P<.01$	C > L; H = L; C = H
Psychological Reward	0.3; ns	1.7; ns	6.8; $P<.01$	C > L; H = L; C = H
Negative Effects	0.4; ns	0.8; ns	4.2; $P<.02$	C > L; H > L; C = H

Values of F of repeated-measures ANOVA are shown; where there was a significant main effect, post hoc pairwise comparisons (Bonferroni) between cigarettes were made. C = commercial; H = research, high yield, L = research, low yield, ns = nonsignificant.

Data from the Cigarette Evaluation Scale (Westman et al., 1992) are shown in the lower half of Table 1. On the cigarette satisfaction question, there was a significant effect of cigarette and a group by cigarette interaction; there was no significant main effect of group (menthol vs. nonmenthol). Satisfaction scores were significantly greater after smoking commercial or high-yield nicotine research cigarettes than the low-yield research cigarette. There was no difference between the commercial and the high-yield research cigarettes. The nonmenthol high-yield cigarette was rated higher than the menthol high-yield cigarette. An ANOVA using ethnicity and cigarette as main factors revealed that there was no significant effect of ethnicity or significant interaction between ethnicity and cigarette type.

The Craving Relief question indicated a significant effect of cigarette and a significant group by cigarette interaction; there was no significant main effect of group. The craving relief score was significantly higher after smoking commercial and high-yield research cigarettes than after low-yield research cigarettes. There was no significant difference between the commercial cigarette and the high-yield research cigarette. The high-yield research cigarette was more effective at reducing craving among the nonmenthol group. An ANOVA using ethnicity and cigarette as main factors revealed a significant effect of cigarette [$F(2,33)=13.8$, $P<.01$], no significant main effect of ethnicity but the interaction between ethnicity and cigarette type was significant [$F(2,68)=7.0$; $P<.01$]. African Americans obtained more craving relief from the low-yield and less from the high-yield cigarettes than white subjects.

On scales that measured Peripheral Sensation, Psychological Reward and Negative Effects, a similar pattern of results occurred. There were significant main effects of cigarette but no significant main effect of group and no significant group by cigarette interaction. On all scales, the scores after smoking the commercial cigarette were significantly higher than after the low-yield research cigarette. Scores after smoking the commercial and the high-yield research cigarettes did not differ. On the scales of Peripheral Sensation and Psychological Reward, the high- and low-yield research cigarettes were not different; but on the negative effects scale, scores after smoking the high-yield cigarette were significantly higher than after the low-yield cigarette.

4. Discussion

The principal aim of this study was to determine how nicotine delivery (assessed by FTC methods) and menthol flavoring of cigarettes interact to influence physiologic and subjective effects of smoking. Since a large portion of smokers in the United States choose mentholated cigarettes (Cummings et al., 1987; Orleans et al., 1989; Sidney et al., 1979), it is important to assess research cigarettes that meet the flavor preferences of this population of smokers.

Consistent with previous research, cigarettes that contained nicotine increased HR and SBP and DBP compared to the low-yield nicotine cigarettes (Butschky et al., 1995; Pickworth et al., 1999; Rose and Behm, 1991). Additionally, the present study showed that the menthol condition did not significantly affect cardiovascular parameters. This lack of effect of mentholation in the low-yield cigarettes replicates the recent findings by Pritchard et al. (1999) who reported that menthol in a denicotinized cigarette had no subjective or physiologic effects. The results of the present study extend those findings to indicate that mentholation does not significantly change the effects of smoking cigarettes that deliver average and higher amounts of nicotine.

The study population reflected the consumption preferences of adult US smokers. African American smokers frequently choose menthol cigarettes, whereas white smokers frequently choose nonmentholated cigarettes (Cummings et al., 1987; Orleans et al., 1989; Sidney et al., 1979). However, ethnic differences in group composition (i.e., the overrepresentation of African American smokers in the menthol group) may have impacted the present results.

For example, ethnic differences in nicotine metabolism could have been operative. Caraballo et al. (1998) reported higher levels of cotinine, the major metabolite of nicotine, in African Americans compared with white and Mexican Americans, at all levels of cigarette consumption. Sellers (1998) suggested that the differences in cotinine could be due to ethnic differences in the distribution of polymorphic varieties of *CYP2A6*, a gene that controls the production of the enzymes involved in nicotine metabolism. Where significant differences between the cigarettes were revealed, the analyses were repeated using ethnicity as a main factor. No main effects of ethnicity were significant, but there was a significant interaction between ethnicity and cigarette type on the craving relief measure where African Americans obtained more craving relief from the low-yield and less from the high-yield cigarettes than white subjects.

Smoke delivery factors such as time to smoke and puffs per cigarette were different for the research cigarettes compared to the commercial cigarettes. These results indicate that the manufacturing process of the research cigarettes, and not their nicotine delivery or mentholation, affected the way the cigarettes were smoked. Manufacturing characteristics (e.g., density of tobacco packing, paper porosity) that influence physical characteristics of cigarettes could affect the texture and draw from cigarettes (Pickworth et al., 1998; Scherer, 1999) resulting in longer time to smoke and more puffs to smoke.

The effects of the cigarettes were assessed on subjective measures of satisfaction, perceived strength, craving relief, peripheral sensation, psychological reward and negative effects. The overall trend was that nicotine delivery, but not menthol flavoring, determined subjective ratings of strength. Nicotine has been shown to play an important sensory role in cigarette taste and sensory impact (Pritchard et al., 1996). Subjective measures likely reflect nicotine and tar content and cigarette properties (air dilution, draw, taste, heat). The interaction between nicotine and tar delivery must be evaluated in studies where plasma levels of nicotine and smoking topography measures are collected.

Some of the peripheral sensations induced by smoke-delivered nicotine may be mediated at nicotine receptors exist along the airways (Grant et al., 1986; Lee et al., 1993). The peripheral effects of nicotine were demonstrated in a recent study that distinguished the nicotine from the non-nicotine components of tobacco smoke (Rose et al., 2000). Nicotine activated sensory nerves in animal (Ginzel, 1975) and human studies (Rose et al., 1993). Chronic nicotine administration is known to increase the number of brain nicotine receptors (Marks et al., 1992; Benwell et al., 1988), but the effects of chronic nicotine administration on the number of nicotine binding sites in peripheral tissue lining the airways is unknown. It is likewise uncertain whether the subjective effects of cigarettes (e.g., taste, strength, satisfaction) differ as a function of the level of nicotine tolerance.

The high-yield research cigarettes in the study delivered (by FTC machine estimates) about twice the nicotine and considerably more tar than commercial cigarettes. Nevertheless, the responses to the high-yield research cigarettes and the commercial cigarettes were similar and usually differed from the low-yield cigarette. Evidently, subjective evaluations of cigarette taste and strength may depend upon a threshold level of nicotine or other components of tobacco smoke. Very low levels of delivery are regarded as unsatisfactory, but higher (than usual) delivery does not increase satisfaction and, at some level, may have been aversive.

McCarthy et al. (1995) reported an exhaled CO and cardiovascular effects were similar after nonmenthol and menthol cigarettes but when nonmenthol smoking was associated with larger puff volumes and more puff per cigarette. In the present study, exhaled CO and HR changes were similar in menthol and nonmenthol cigarettes. However, in the present study, topography measures were not related to nicotine or menthol but appeared dependent on the manufacturing differences between research and commercial cigarettes.

Further studies of these research cigarettes are warranted. Plasma nicotine levels after smoking the research and commercial cigarettes would indicate whether differences between cigarettes are due to pharmacologic or manufacturing components. The present study compared commercial and research, menthol and nonmenthol cigarettes using groups that ordinarily smoke either menthol or nonmenthol cigarettes. This experimental design led to ethnic differences in group composition. Although statistical corrections were applied to correct for ethnic differences, it would be desirable to also study the cigarettes in ethnically homogenous groups or using a within-subjects design. Nevertheless, using the new high- and low-yield research cigarettes, it was determined that nicotine content, but not mentholation, importantly determined the physiologic and subjective effects of smoking. The research cigarettes used in the present study may prove useful in smoking studies where a wide range of nicotine delivery is needed.

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