The Effect of Menthol Vapor on Nasal Sensitivity to Chemical Irritation

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Received December 17, 2010; accepted April 25, 2011

Abstract

Introduction: Among other effects, menthol added to cigarettes may modulate sensory response to cigarette smoke either by masking “harshness” or contributing to a desirable “impact.” However, harshness and impact have been imprecisely defined and assessed using subjective measures. Thus, the current experiments used an objective measure of sensitivity to chemical irritation in the nose to test the hypothesis that menthol vapor modulates sensitivity to chemical irritation in the airways.

Methods: Nasal irritation thresholds were measured for 2 model compounds (acetic acid and allyl isothiocyanate) using nasal lateralization. In this technique, participants simultaneously sniff clean air in one nostril and chemical vapor in the other and attempt to identify the stimulated nostril. People cannot lateralize based on smell alone but can do so when chemicals are strong enough to feel. In one condition, participants were pretreated by sniffing menthol vapor. In a control condition, participants were pretreated by sniffing an odorless blank (within-subjects design).

Results: Pretreatment with menthol vapor decreased sensitivity to nasal irritation from acetic acid (participants required higher concentrations to lateralize) but increased sensitivity to allyl isothiocyanate (lower concentrations were required).

Conclusions: The current experiments provide objective evidence that menthol vapor can modulate sensitivity to chemical irritation in the upper airways in humans. Cigarette smoke is a complex mixture of chemicals and particulates, and further work will be needed to determine exactly how menthol modulates smoking sensation. A better understanding could lead to treatments tailored to help menthol smokers quit by replacing the sensation of mentholated cigarettes.

Introduction

Menthol is added to approximately 26% of cigarettes sold in the United States (Giovino et al., 2004). However, the U.S. Food and Drug Administration recently banned most flavor additives in cigarettes and is now considering regulation of menthol (Richwine, 2010). Blacks are both more likely to smoke mentholated cigarettes and more likely to die from lung cancer than their White counterparts (Richardson, 1997), though most epidemiological studies that have controlled for race and other demographic factors have found that smokers of mentholated and nonmentholated cigarettes have similar health outcomes (see Mendiondo, Alexander, & Crawford, 2010). Interestingly, despite similar health outcomes, menthol smokers tend to smoke fewer cigarettes per day (Fagan et al., 2010; Mendiondo et al., 2010), so the question of whether menthol increases risk remains open.

Menthol could increase oral absorption of nicotine (Squier, Manzt, & Wertz, 2010), affect physiological responses to nicotine, at least in young animals (Ruskin, Anand, & LaHoste, 2008), and affect nicotine metabolism (Benowitz, Herrera, & Jacob, 2004). These effects could play a role in smoking initiation, addiction, and cessation. Indeed, use of mentholated cigarettes might be associated with greater dependence (according to some measures) and lower quitting rates, especially in non-White populations (Ahijevych & Ford, 2010; Fagan et al., 2010; Gandhi, Foulds, Steinberg, Lu, & Williams, 2009; Stahre, Okuyemi, Joseph, & Fu, 2010; Trinidad, Perez-Stable, Messer, White, & Pierce, 2010; but also see Alexander, Crawford, & Mendiondo, 2010; Hyland, Garten, Giovino, & Cummings, 2002). Sensory properties of menthol could also play a role in smoking behavior and addiction (Fowles & Shusterman, 2004; Kreslake, Wayne, & Connolly, 2008).

Cooling is perhaps the most salient sensory effect of menthol, with irritation at higher levels (Cliff & Green, 1994, 1996; Dessirier, O’Mahony, & Carstens, 2001). Menthol also stimulates taste and smell (Nagata, Dalton, Doolittle, & Breslin, 2005). Menthol sensation could gain reward value through association with the pharmacological effects of nicotine (Rose & Behm, 2004) but may also be desirable in its own right (Fowles & Shusterman, 2004; Kreslake et al., 2008; Unger, Allen, Leonard, Wenten, & Cruz, 2010). Furthermore, tobacco companies have long believed that adding menthol to cigarettes can reduce the “harshness” of tobacco smoke (Wood, 1959). Sensory research by the tobacco industry suggests that menthol can either reduce or enhance the “impact” of tobacco smoke depending on levels of both menthol and nicotine in cigarettes (Hayes, Martin, & Gulotta, 1995).

doi: 10.1093/ntr/ntr107
Advance Access published on June 7, 2011
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However, “impact” in industry work was measured via subjective ratings and was not precisely defined. Since both menthol and cigarette smoke can stimulate taste, smell, and somatosensation (Fowles & Shusterman, 2004; Nagata et al., 2005), the basis of the sensory effects of menthol on perception of tobacco smoke remains unclear. According to one hypothesis, menthol works in part by masking the somatosensory impact of tobacco smoke (Fowles & Shusterman, 2004). Sensory irritation, for example, stinging, burning, prickling, or pungency, helps protect the sensitive airways by warning of high concentrations of chemicals, including the aldehydes, organic acids, and nicotine present in tobacco smoke (Ayer & Yeager, 1982; Bryant & Silver, 2000; Fowles & Shusterman, 2004).

Importantly, relevant behavioral data are sparse, particularly from humans. Application of relatively high (irritating) concentrations of menthol desensitizes the tongue to irritation from subsequent applications of menthol and also desensitizes the tongue to irritation from capsaicin (which gives hot peppers their burn), nicotine, and cinnamaldehyde (Cliff & Green, 1996; Dessier et al., 2001; Green & McAluliffe, 2000; Klein, Carstens, et al., 2011). In contrast to oral irritation, the literature offers very little information on how menthol interacts with chemical irritants in the airways. Some evidence suggests that inhalation of menthol vapor increases the concentration of citric acid needed to evoke coughing, consistent with purported antitussive effects (Morice, Marshall, Higgins, & Grattan, 1994; but also see Kenia, Houghton, & Beardmore, 2008). The relationship between cough sensitivity and sensitivity to chemical irritation is unclear.

The current study assessed the effect of menthol on sensitivity to nasal irritation in humans. It is unclear whether nasal irritation is a particularly important component of smoking sensation. However, nasal irritation has two key advantages as a model. First, the respiratory epithelium that lines the nasal cavity is similar in structure and function to the epithelium that lines most of the airways (Baroody & Canning, 2003). Second, the anatomical separation between the two sides of the nose allows a spatial forced-choice detection paradigm with vapor-phase stimuli, that is, nasal lateralization.

In nasal lateralization, participants simultaneously receive chemical vapor in one nostril and clean air in the other. Participants attempt to determine which nostril received chemical vapor. Humans cannot lateralize odors but can lateralize chemical vapor once concentrations reach levels high enough to feel (Frasnelli, Charbonneau, Collignon, & Lepore, 2009; Kobal, Van Toller, & Hummel, 1989; Wysocki, Cowart, & Radil, 2003). This method provides an objective assessment of sensitivity. Lateralization thresholds for two model irritants (acetate acid and allyl isothiocyanate) were assessed both after preexposure to the headspace above a menthol solution and after preexposure to a blank (odorless solvent). The main hypothesis was that exposure to menthol would increase lateralization thresholds for (decrease sensitivity to) nasal irritation.

Experiment 1

Purpose

Experiment 1 assessed the impact of preexposure to menthol vapor on sensitivity to nasal irritation from acetic acid, the primary flavor component of white vinegar. Acetic acid is present in cigarette smoke (Ayer & Yeager, 1982). Since acetic acid is also present in many foods and beverages and ubiquitous in indoor air, acetic acid has wide interest as a model irritant.

Materials and Methods

Participants

Twenty-two (14 female and 8 male) adults (21–46 years of age; mean = 30.5, SD = 7.0) participated. All were healthy by self-report. Six were smokers who participated in a pilot test to select an appropriate concentration for the menthol pretreatment stimulus. The other 16 were nonsmokers who participated in the main experiment. Participants were recruited from the local Philadelphia area and paid for participation. Before testing, participants provided written informed consent on forms approved by an Institutional Review Board of the University of Pennsylvania.

Menthol Preexposure Stimulus

L-Menthol (CAS# 2216-51-5, Sigma-Aldrich) was dissolved in filtered light mineral oil and presented in 250-ml glass sniff bottles (10 ml of solution was placed in a bottle). The caps of the bottles had both an inlet tube that terminated about 1 cm above the surface of the solution and a sniffing aperture to which Teflon nose pieces were attached. Six identical sniff bottles were prepared to avoid depletion of the solutions, and fresh solutions were prepared weekly. In addition, six similar bottles that contained only 10 ml of mineral oil were prepared to provide control (blank) preexposure.

The menthol concentration was selected to have a sensory impact comparable with the menthol in a popular cigarette band (Kool). Six regular smokers of nonmentholated cigarettes (23–37 years old, half female) smoked a Kool cigarette for about 30 s. Participants were instructed to smoke according to their usual habits. Smoking topography was not regulated, but participants held the cigarette under and exhaled into a fume hood. After a 10-min pause, participants inhaled headspace from a series of menthol concentrations and selected the concentration that best matched the menthol sensation that they experienced while smoking. Concentrations ranged from 250.0 (Step 0) to 1.0 mg/ml in six threefold dilution steps. The average of the steps selected as the best match was 1.5, which corresponds to a target concentration approximately 48.1 mg/ml. The actual menthol pretreatment solution used in the experiment was 48.9 mg/ml. A sensory matching approach was chosen because the impact of most chemical stimuli depends on the method and dynamics of delivery (Wise, Zhao, & Wysocki, 2009), so adjusting the concentration in a sniff bottle to match the concentration in a cigarette may not result in equal (or even comparable) perceived intensity.

Model Irritant

Acetic acid (CAS# 64-19-7, Sigma-Aldrich) was dissolved in odorless propylene glycol. The highest step (Step 0) was the concentration of typical vinegar, viz., 5.0% (vol/vol). Concentrations decreased in 11 binary dilution steps down from Step 0 to 0.002% (vol/vol). Solutions were presented in the same type of sniff bottles used for the menthol pretreatment (as described in the preceding section). Multiple instances of each concentration were prepared weekly to avoid depletion of solution. Multiple bottles that contained 10 ml of pure propylene glycol were also prepared to serve as blanks in nasal lateralization trails (see “Procedure” below).
Calibration of Acetic Acid Concentration

Experimenters prepared a series of dilutions identical to those used to measure lateralization thresholds, except that bottles were sealed with septum caps (Teflon-coated silicon septa) for syringe insertion. All headspace measurements were made at room temperature after manual agitation identical to that used in subject testing. Headspace samples were withdrawn using a 10-μl gas-tight syringe.

After insertion of the syringe, the plunger was withdrawn and inserted (“pumped”) three times, and a sample of 5 μl was withdrawn for injection into a gas chromatography–mass spectrometry (GC/MS) system (Thermoquest GC/MS, with Xcalibur software, from ThermoElectron Corp., San Jose, CA). A polar Stabilwax column, 30 M × 0.32 mm with 1.0 μ coating (Restek Corp., Bellefonte, PA), was used for separation. Helium carrier gas flowed at a constant rate of 2.5 ml/min. Injections were made into the chromatograph’s injector, which was heated to 230 °C. The initial column temperature of 60 °C was held for 4 min, then increased by 6 °C/min to a final temperature of 220 °C. Headspace injections were repeated at least three times at each concentration to obtain average peak area for acetic acid. These peak areas were converted to concentration (parts per million [ppm] by mass) using a calibration curve based on injection of known masses of acetic acid in liquid phase: 0.1, 0.05, 0.025, 0.01, 0.001, and 0.0001 mg/ml, diluted in chloroform. Each liquid solution was injected three times.

Measurements were obtained from dilution Step 0 down to Step 6, which captured the range of threshold concentrations for all participants. Headspace concentrations of successive dilution steps differed by about 2.2-fold. At lower concentrations, measurements of headspace concentration became unreliable. Lower concentrations were estimated by extrapolation. Concentrations for the 12 stimuli (ppm by mass) follow: 377.1, 170.3, 76.8, 34.7, 15.6, 7.05, 3.18, 1.43, 0.65, 0.29, 0.13, and 0.06.

Procedure

In each experimental trial, participants began by taking three natural sniffs (about 1 s in duration) of a pretreatment stimulus. Two bottles (one for each nostril), sniffed simultaneously, provided the stimulus. In some experimental sessions, the bottles contained only mineral oil (control condition). In other sessions, the bottles contained menthol solution (menthol pretreatment). Approximately 2 s separated the sniffs. Approximately 3 s after the last sniff of the pretreatment stimulus, participants took one natural sniff from another pair of bottles (again, one bottle for each nostril). One bottle contained only propylene glycol (blank), and the other bottle contained an acetic acid solution (target to be lateralized). The nostril that received acetic acid (left or right) varied randomly from trial to trial. Participants were instructed to determine which nostril received the acetic acid, guessing if uncertain. Participants also rated their confidence in the correctness of each response on a scale of 0 (total guess) to 3 (absolutely sure).

Thresholds for lateralization were measured using an ascending method of limits (Wysocki & Wise, 2003). For the first trial in a threshold test, a weak acetic acid concentration that caused no nasal irritation was presented. After an incorrect response, that is, the participant chose the nostril that did not receive acetic acid, concentration increased by a single twofold dilution step. After a correct response, the same concentration was presented again. One minute separated successive trials. In this fashion, concentration of acetic acid increased until the participant was able to correctly lateralize a given dilution step in four consecutive trials. We added the additional criterion that each response must be given with a confidence of at least “two” because the probability of four consecutive correct responses at any given concentration is 0.063 by chance alone. When both criteria were met (which almost always occurred at the same concentration), the threshold test ended and the last concentration presented was defined as threshold.

Participants completed five experimental sessions, with 1–3 days elapsing between sessions. In the first session, participants completed 10 lateralization trials with the menthol pretreatment stimulus (fixed concentration). Participants also rated the intensity of cooling, burning, and stinging from the menthol stimulus using a labeled magnitude scale (gLMS; Bartoshuk et al., 2004). These brief sensory tests introduced participants to the menthol pretreatment stimulus and provided data on how the stimulus was perceived. During the first session, participants also completed a single acetic acid lateralization threshold test (without use of a pretreatment stimulus). The results of this initial test were used to select starting concentrations for threshold tests in the subsequent four sessions.

In each of the following four experimental sessions, participants completed two (replicate) threshold tests separated by a break of at least 15 min. Each threshold test began with a concentration five dilution steps below the acetic acid threshold measured in the first session. Measured thresholds were higher than this starting point in all cases. The same pretreatment stimulus was used in both threshold tests within a session. The pretreatment stimulus varied across sessions in blocked random order. Participants completed tests for the menthol and control pretreatment conditions in random order for Sessions 2 and 3, then again in random order for Sessions 4 and 5. Thus, the design included a built-in replication for each condition. The design was completely within participants (all participants completed all conditions).

Data Analysis

One participant failed to complete all sessions and was therefore excluded from analysis. For the remaining 15 participants, replicate threshold measurements (within experimental sessions) were averaged and submitted to a repeated measures analysis of variance (ANOVA). The ANOVA was conducted using Statistics software (Version 9.0, Statsoft), with a significance criterion of p < .05. There were two factors: block (Sessions 2 and 3 vs. Sessions 4 and 5) and pretreatment (menthol vs. control). Simple effects were evaluated using contrasts with a Bonferroni correction for multiple comparisons.

Results

Sensory Characteristics of the Menthol Pretreatment Stimulus

On average, participants correctly lateralized the menthol pretreatment stimulus in 9.27 of 10 trials (SEM = 0.29). According to binomial statistics (criterion of p < .05), only one participant (who correctly lateralized in only 6/10 trials) failed to achieve reliable lateralization performance. These results suggest that the menthol pretreatment stimulus was strong enough to feel.

Intensity ratings for sensory qualities appear in Figure 1. Single-sample t tests revealed that ratings for burning, stinging,
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Figure 1. Rated sensory intensity of the pretreatment stimulus (y-axis) for three sensory qualities (x-axis). Rated qualities included “burn,” “sting,” and “cooling.” The letters along the y-axis represent intensity descriptors: W = “weak,” M = “moderate,” S = “strong,” and VS = “very strong.” Error bars represent ± SEM.

and cooling were all significantly ($p < .05$) greater than zero. A one-way ANOVA (with rated quality as the factor) revealed significant difference in the magnitudes of the rated qualities, $F(2, 28) = 13.30, p < .0001, \eta^2_p = 0.49$. Bonferroni-corrected contrasts revealed that ratings of cooling were significantly stronger than those of both burning and stinging, but the difference between burning and stinging failed to reach statistical significance. In short, participants rated the pretreatment stimulus as having some burn and sting but rated cooling as the predominant sensation quality.

The Effect of Menthol Pretreatment
Relative to the control condition (blank pretreatment), pretreatment with menthol made participants less sensitive to nasal irritation from acetic acid. In other words, a higher concentration of acetic acid was required for reliable lateralization after menthol pretreatment (Figure 2). The two blocks of sessions gave comparable results. ANOVA confirmed these impressions. The main effect of pretreatment reached significance, $F(1, 14) = 32.08, p < .0001, \eta^2_p = 0.70$. The main effect of block and the two-way interaction failed to reach significance ($p > .55$). Post-

hoc tests revealed that both menthol pretreatments resulted in elevated acetic acid thresholds relative to both control pretreatment thresholds but that neither the menthol nor the control thresholds differed between blocks. The test–retest correlation between the two sessions (Pearson’s $r$) was $0.61 (p < .02)$ for thresholds measured with the control pretreatment and $0.81 (p < 0.001)$ for the menthol pretreatment. Regarding the absolute magnitude of the effect, menthol pretreatment caused an 102% increase in the threshold for acetic acid.

Figure 2. Thresholds for nasal lateralization of acetic acid (y-axis, log parts per million [ppm] by mass) for the first and second blocks of trials. Filled bars represent thresholds after sniffing a menthol pretreatment. Open bars represent thresholds after sniffing an odorless (solvent) blank. Error bars represent ± SEM.

Experiment 2

Purpose
Preexposure to menthol reduced sensitivity to nasal irritation from acetic acid in Experiment 1. However, it is unclear whether this effect generalizes to other irritant compounds. The goal of Experiment 2 was to examine the effects of menthol on sensitivity to nasal irritation from an additional model irritant, allyl isothiocyanate. This compound contributes to the distinctive bite of mustard and horseradish. Allyl isothiocyanate is not known to be an important irritant in tobacco smoke, but it is a potent agonist of the TRPA1 receptor protein expressed in sensory nerves in the airways (Bessac & Jordt, 2010). Since TRPA1 also responds to important irritants in cigarette smoke, including nicotine, crotonaldehyde, and acrolein (André et al., 2008; Talavera et al., 2009), allyl isothiocyanate is a relevant model irritant that is safe to present to nonsmokers.

Materials and Methods
In most respects, the procedures exactly matched those of Experiment 1. Fifteen (10 female and 5 male) adults (21–46 years of age; mean = 29.3, $SD = 7.0$) participated. All were healthy by self-report. Six had participated in Experiment 1.

The pretreatment stimulus was the same as in Experiment 1, but the model irritant was allyl isothiocyanate (CAS# 57-06-7, Sigma-Aldrich, 95% pure) dissolved in filtered light mineral oil. The highest concentration (Step 0) was 1.0% (vol/vol). Concentrations decreased in fourteen 1.5-fold dilution steps down to 0.003% (vol/vol). Smaller dilution steps were used for allyl isothiocyanate than for acetic acid because pilot work indicated that the transition to reliable lateralization was sharper. Headspace was measured as described for Experiment 1. Reliable measurements were made down to dilution Step 8, which captured the range of threshold concentrations for all but one participant. Headspace concentrations of successive dilution steps differed by about 1.7-fold. At lower concentrations, measurements of headspace concentration became unreliable, so lower concentrations were estimated by extrapolation. Concentrations for the 15 stimuli (ppm by mass) follow: 565.4, 325.3, 187.1, 107.6, 61.9, 35.6, 20.5, 11.8, 6.78, 3.90, 2.24, 1.29, 0.74, 0.43, and 0.25.

Other details of stimulus preparation and presentation were the same as in Experiment 1. Methods of data analysis also were the same as in Experiment 1. One participant was unable to lateralize the highest concentration of allyl isothiocyanate (in fact seemed not to be sniffing in a consistent fashion despite instructions) and was therefore excluded from the analyses of the effect of menthol on lateralization.
Results

Sensory Characteristics of the Menthol Pretreatment Stimulus

Results were comparable with those from Experiment 1. On average, participants correctly lateralized the menthol pretreatment stimulus on 9.71 of 10 trials (SEM = 0.16), suggesting that participants could feel the stimulus in the nose. All participants showed significantly reliable lateralization according to binomial statistics. Ratings for burning, stinging, and cooling were all significantly greater than zero (p < .05). Again (data not shown), ANOVA revealed a main effect of rated quality: F(2, 26) = 18.37, p < .0001, η² = 0.59. Bonferroni-corrected contrasts revealed that ratings of cooling were significantly stronger than those of both burning and stinging, but the difference between burning and stinging failed to reach statistical significance. Thus, participants rated the pretreatment stimulus as predominately cooling but also rated it as having some burn and sting.

The Effect of Menthol Pretreatment

Relative to the control condition (blank pretreatment), pretreatment with menthol made participants more sensitive to nasal irritation from allyl isothiocyanate. In other words, a lower concentration of allyl isothiocyanate was required for reliable lateralization after menthol pretreatment (Figure 3). The two blocks of sessions gave comparable results. ANOVA confirmed these impressions. The main effect of pretreatment reached significance; F(1, 13) = 13.25, p < .005, η² = 0.52. The main effect of block and the two-way interaction failed to reach significance (p > .77). Post-hoc tests revealed that both menthol pretreatments resulted in lower allyl isothiocyanate thresholds relative to both control pretreatments but that neither the menthol nor the control thresholds differed between blocks. The test–retest correlation between the two sessions (Pearson’s r) was .80 (p < .001) for thresholds measured with the control pretreatment and .86 (p < .001) with the menthol pretreatment. Regarding the absolute magnitude of the effect, menthol pretreatment caused a 47% decrease in the threshold for allyl isothiocyanate.

Discussion

Preexposure to a level of menthol vapor matched in sensory impact to a high menthol content cigarette reduced sensitivity to nasal irritation from acetic acid (increased lateralization thresholds by about 102%) but increased sensitivity to nasal irritation from allyl isothiocyanate (decreased lateralization thresholds by about 47%). These experiments provide objective evidence that menthol preexposure modulates sensitivity to chemical irritation in the nasal cavity in humans. Furthermore, these results suggest that the impact of menthol preexposure is compound specific and that menthol can either enhance or reduce sensitivity under the conditions of these experiments.

Implications for Smoking Behavior

Chemical stimulation of somatosensory nerves in the airways is a key contributor to the bite of tobacco smoke (Fowles & Shusterman, 2004). Thus, sensory irritation probably plays an important role in the “harshness” of cigarette smoke that menthol is believed to mask. Topical application of menthol to the skin has anesthetic and antinociceptive effects (Galeotti, Di Cesare Mannelli, Mazzanti, Bartolini, & Ghelardini, 2002; Galeotti et al., 2001; Klein, Sawyer, et al., 2010), and pretreatment of the tongue with relatively high concentrations of menthol decreases ratings of oral irritation from subsequent applications of other irritants (Cliff & Green, 1996; Dessirier et al., 2001; Green & McAuliffe, 2000; Klein, Carstens, et al., 2011). Thus, the idea that menthol added to cigarettes might dull nociceptive responses to irritants is plausible. However, the current results, under conditions that more closely approximate airway exposure during smoking, are not consistent with simple anesthesia or analgesia. Menthol could either reduce or enhance sensitivity.

The fact that the menthol pretreatment was matched to a high menthol brand may have relevance. Masking of the harshness of cigarette smoke may be particularly important for young beginning smokers, who generally prefer low menthol brands (Kreslake et al., 2008). Future work can determine if lower levels of menthol than were used in the current experiments reduce sensitivity more uniformly. The current results may have more relevance to experienced smokers, particularly many Blacks, who often enjoy strong menthol sensation and tend to prefer brands higher in menthol (Kreslake et al., 2008).

Though the menthol pretreatment stimulus was predominantly cooling, participants did report that it had some burn and sting. This finding is consistent with the idea that menthol could contribute directly to the “bite” that is an integral part of the sensory response to cigarettes. In addition, the work provides objective evidence that menthol can modulate sensitivity to other chemical irritants. Cigarette smoke is a complex mixture of chemicals and particulate matter. Menthol may alter the feel of smoke by enhancing sensitivity to some compounds and reducing sensitivity to others. In a recent study of Black menthol smokers, taste/feel was cited as an important reason for smoking mentholated cigarettes, particularly among women (Allen, Cruz, Leonard, & Unger, 2010). Further work along the lines of the current experiments can help us understand the details of how menthol interacts with other compounds to produce the unique sensory impact of mentholated cigarettes. A better understanding of the relationship between stimulus and...
sensation can help us formulate cessation aids, tailored to smokers of mentholated cigarettes, which make it easier to quit by simulating the flavor and feel of a mentholated cigarette.

Sensory Mechanisms

Menthol is an agonist of TRPM8, a transient receptor potential channel in sensory nerves that is involved in the perception of both innocuous cooling and cold pain (Green & Schoen, 2007; Knowlton, Bifolck-Fisher, Bautista, & McKemy, 2010; McKemy, Neuhausser, & Julius, 2002; Peier et al., 2002). Thus, TRPM8 almost certainly plays a role in perceived cooling of menthol and may play a role in its bite as well. Menthol also acts on other receptors in sensory nerves, including TRPA1 (MacPherson et al., 2006). As mentioned previously, TRPA1 responds to various chemical irritants, including allyl isothiocyanate (Andrè et al., 2008; Bessac & Jordt, 2010; Talavera et al., 2009). Interestingly, the action of menthol on TRPA1 may be bimodal such that low concentrations activate the channel and high concentrations reversibly block it (Karashima et al., 2007; but also see Xiao et al., 2008). In Experiment 2, menthol pretreatment may have resulted in low levels of menthol in the nasal mucosa that activated TRPA1 in cooperation with allyl isothiocyanate, lowering irritation thresholds. The transduction mechanisms for irritation from acetic acid are unclear, but acetic acid does not seem to be a TRPA1 agonist (Bessac et al., 2008; but also see Wang, Chang, & Liman, 2010), which could help explain the difference in outcomes for the two model irritants in these experiments.

Limitations

Though a sensory matching technique was used to select a menthol level for pretreatment, other stimuli in the cigarette smoke, for example, irritant chemicals and particulates, could have influenced perceived menthol impact in cigarettes or made it difficult for participants to focus on menthol impact. Future studies should examine a range of menthol pretreatments to achieve a fuller understanding of the effect of concentration.

In addition, though the current experiments may approximate airway exposure during smoking more closely than do topical application of menthol to the tongue and skin, the current methods do not mimic smoking perfectly. In smoking, menthol is presented simultaneously with other irritant stimuli rather than used as a pretreatment. The dynamics of airway sensitivity to chemical irritants have received relatively little attention, but the pattern of stimulation over time clearly matters (Wise et al., 2009). For example, one sniff of allyl isothiocyanate may feel either more or less intense than the last depending on elapsed time between sniffs (Brand & Jacquot, 2002). Dynamics, and the difference between simultaneous and successive presentation in particular, deserve more attention. Furthermore, smokers do not typically sniff cigarette smoke, and further experiments will be needed to determine whether these results generalize to other parts of the airways. In short, the current experiments employed a well-controlled model of nasal irritation with an objective outcome-measure, but further work will be needed to determine how well the results generalize to cigarette smoking.

Additional work also will be needed to determine how well the results generalize to other irritants, including nicotine and actual cigarette smoke. It is relatively easy to control the concentrations of acetic acid and allyl isothiocyanate, and these compounds are relatively safe as presented. Presenting nicotine and cigarette smoke to nonsmokers can be problematic for ethical reasons. Presenting cigarette smoke to smokers would be less problematic. Of course, smokers may differ from nonsmokers in their responses to menthol (and smokers of mentholated cigarettes might differ from smokers of nonmentholated cigarettes). Though we know of no published work that has examined the relationship between smoking status and subjective measures of sensory response to menthol, published work does suggest that smokers and nonsmokers may differ in their sensory responses to other chemical stimuli (Katotomichelakis et al., 2007; Thurauf, Kaegler, Renner, Barocka, & Koba, 2000; Vennemann, Hummel, & Berger, 2008). We chose to focus on nonsmokers in the current work to keep the experiments as simple as possible. However, future work should examine how smoking status interacts with menthol exposure to modulate sensitivity.

Funding

This work was supported by institutional funds.

Declaration of Interests

None declared.

Acknowledgments

We thank Ms. Rebecca Lapinski, Ms. Elizabeth O’Brien, and Ms. Jennifer Louie for excellent technical assistance.

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