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Brief Report

Menthol Preference Among Smokers: Association With *TRPA1* Variants

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Abstract

Introduction: Preference for smoking menthol cigarettes differs from individual to individual and population to population in ways that may provide higher levels of nicotine intake and contribute to smoking's morbidity and mortality. Menthol acts at sites that include the transient receptor potential (TRP) A1 channel that is expressed by nociceptors in the lung and airways, suggesting that individual and population differences in *TRPA1* sequences might contribute to observed differences in menthol preference among smokers.

Methods: We have thus sought association between menthol preference and common variants in the *TRPA1* gene in heavier and lighter European-American smokers. Smokers were recruited for studies of smoking cessation in North Carolina and of substance abuse genetics in Maryland.

Results: A common *TRPA1* haplotype is defined by 1 missense and 10 intronic single nucleotide polymorphisms that display significant ($.006 < p < .05$; χ^2) association with preference for mentholated cigarettes in heavy smokers (odds ratio ca. 1.3). There are smaller trends in the same direction in lighter smokers.

Conclusions: This *TRPA1* haplotype provides a novel biological basis for individual differences in menthol preference and possibly for actions of other agents that act at *TRPA1*.

Introduction

Among smokers, there are substantial individual differences in preference for mentholated brands of cigarettes (Kreslake, Wayne, & Connolly, 2008). There are also differences in the fraction of menthol-containing cigarettes that are sold to and smoked by individuals with different racial/ethnic backgrounds. There are higher levels of sales and consumption in many Asian and African-American communities than in communities of European descent, although many individuals of European descent also display strong preferences for mentholated cigarettes (Appleyard, Messeri, & Haviland, 2001; Hooper et al., 2011; Lawrence et al., 2010; Osaki et al., 2006).

Sociologic explanations have been offered for menthol preference. Attention has been focused on the ways in which advertisement and promotions have been aimed at communities with higher proportions of individuals of African or Asian descent (Cummings, Giovino, & Mendicino, 1987; Landrine et al., 2005). A priori, biological contributions to individual differences in menthol preference are also plausible. Menthol acts at transient receptor potential (TRP) channels that include the *TRPA1* channel that is extensively expressed by nociceptive primary afferent nerve fibers in the lung and elsewhere (Karashima et al., 2007; Lee, 2010; Simon & Liedtke, 2008). By altering activities of noxious smoke constituents at these TRP channels, menthol might alter smoking. Individuals with menthol preferences modified by *TRPA1* channel gene variants might smoke more cigarettes, smoke cigarettes with higher nicotine yields, extract more nicotine from each cigarette, and/or display greater difficulties in quitting smoking (Bover, Foulds, Steinberg, Richardson, & Marcella, 2008; Foulds, Hooper, Pletcher, & Okuyemi, 2010; Harris et al., 2004; Pletcher et al., 2006).

Menthol effects might thus be sought separately in individuals who smoke more heavily versus those who smoke less. Despite the possible modes through which menthol might modify effects of smoking higher numbers of cigarettes and despite the wide availability of menthol-containing cigarettes, however, only a minority of smokers of European ancestry prefer mentholated cigarettes (Giovino et al., 2004).

We wondered if allelic variants at the *TRPA1* channel might contribute to the individual differences in preference for mentholated cigarettes. We studied individuals of European ancestry, the largest samples available to us and the sample in which power was greatest based on significant numbers of

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menthol-preferring and nonmenthol-preferring smokers. A number of *TRPA1* gene variants display minor allele frequency differences in HapMap samples (http://hapmap.ncbi.nlm.nih.gov/index.html.en) that parallel the racial/ethnic differences in fraction of mentholated cigarettes consumed, providing suggestive evidence for possible roles for allelic variants in this gene in menthol preference. We thus assessed preference for mentholated versus nonmentholated cigarettes in samples of European-American smokers who volunteered for participation in randomized controlled trials of smoking cessation (Raleigh–Durham, NC) and nontherapeutic research in addiction genetics (Baltimore, MD). We studied individuals with high versus low levels of smoking based on available self report data in both samples for smokers of ≥15 versus <15 cigarettes/day. We compared allele frequencies for *TRPA1* single nucleotide polymorphisms (SNPs) in individuals with menthol preference to those who preferred nonmentholated cigarettes.

Methods

Adult subjects were recruited by word of mouth and advertising, reimbursed for participation, and provided written informed consent as approved by Institutional Review Boards at Duke and National Institute on Drug Abuse (NIDA)–Intramural Research Program, respectively. Subjects provided information about their racial/ethnic backgrounds and data concerning their cigarette smoking and brand preference to experienced interviewers. Each individual was characterized as "menthol preferring" and "nonmenthol-preferring" (or indeterminate; these individuals were not included in analyses) by comparing the brand preference to a database of menthol- and nonmenthol-containing cigarettes maintained at the Duke Center for Nicotine and Smoking Cessation Research.

In North Carolina, smokers who expressed desires to quit were recruited for two smoking cessation trials based on inclusion criteria that included self-reported smoking of ≥10 cigarettes/day and end-expired-air CO ≥10 ppm (Rose, Behm, Drgon, Johnson, & Uhl, 2010; Rose, Behm, Westman, & Kukovich, 2006). In Baltimore, smokers were identified among research volunteers for studies of the genetic underpinnings of addictions (Drgon et al., 2010). We thus evaluated DNA from 820 European-American participants whose menthol preference could be determined. There were 122 female and 100 male menthol-preferring heavy smokers (average ages 42 and 40 years, respectively) and 243 and 276 nonmenthol-preferring heavy smokers (44 and 42 years). Corresponding values for light smokers were 16, 9 (34 and 37) and 35, 19 (38 and 31).

DNA was extracted from blood and genotyped using four multiplex primer extension reactions that employed 22, 19, 18, and 3 forward, reverse, and extension primers, respectively, and matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF)–based allele detection (Sequenom, San Diego, CA; primer sequences available from the authors upon request). Each polymerase chain reaction (PCR) reaction contained 1.0 μl genomic DNA (2.5 ng/μl), 0.1 μl dNTP mix (25 mM each), 0.5 μl iPLEX Gold PCR buffer with 20mM $MgCl_2$ (10×), 0.4 μl $MgCl_2$ (25 mM), 1 μl forward and reverse primer mix (500 nM each), 0.2 μl of iPLEX Gold PCR enzyme (5U/μl; Sequenom), and 1.8 μl H_2O. Thermal cycling was (a) 2 min at 94 °C; (b) 45 cycles of 30 s at 94 °C, 30 s at 56 °C, 1 min at 72 °C; (c), 1 min, 72 °C, and (d) then 4 °C. Unincorporated dNTPs were removed by 40 min 37 °C incubation with shrimp alkaline phosphatase, followed by inactivation for 5 min at 85 °C. Extension primers for the 22-plex, 19-plex, and 18-plex assays were adjusted in a 3-tier fashion, dividing primers into low-, medium-, and high-mass groups with final concentrations of 52, 1,040, and 1,570 nM, respectively. The three-plex assay primers were divided into a low-mass group and a high-mass group with final concentrations of 730 and 1,460 nM, respectively. For the high-plex reactions, primer extension was performed with 0.2 μl iPLEX Buffer Plus (10×), 0.2 μl iPLEX termination mix, 0.94 μl extension primer mix (5:10:15 μM), 0.619 μl H_2O, and 0.041 μl iPLEX enzyme (Sequenom). For low-plex reactions, primer extension was performed with 0.2 μl iPLEX Buffer Plus (10×), 0.1 μl iPLEX termination mix, 0.94 μl extension primer mix (7:14 μM), 0.74 μl H_2O, and 0.02 μl iPLEX enzyme. Thermal cycling was carried out as follows: (a) 94 °C for 30s, (b) 40 cycles of (5 s at 94 °C, 5 cycles of [5 s at 52 °C, 5 s at 80 °C]), (c) 3 min at 72 °C, (d) cooling to 4 °C. Reactions were purified with SpectroClean resin (Sequenom), spotted in matrix on Sequenom arrays, and subjected to MALDI-TOF mass spectrographic analyses with automatic allele detection and manual allele confirmation (Sequenom).

Sixty-eight SNPs distributed through *TRPA1* were genotyped. Data from the 51 SNPs that displayed minor allele frequencies >0.05 were analyzed using χ^2 tests, PLINK (pngu.mgh.harvard.edu/~purcell/plink/), and a threshold for nominal significance of $p < .05$ (data available from the authors upon request).

Results

TRPA1 allele frequencies in both samples studied here were similar to those reported in HapMap for individuals of European ancestry. In these samples, as well as in HapMap and/or dbSNP data, haplotypes marked by SNPs with minor allele frequencies of about 0.3 and of about 0.15 extended through much of the length of the *TRPA1* gene.

In the 741 heavy (≥15 cigarettes/day in both samples) smokers, 11 SNPs displayed nominally significant associations with menthol preference ($.006 < p < .048$; Table 1). Menthol preference was uniformly associated with 0.04–0.07 higher minor allele frequencies for the 10 intronic SNPs that provided significant associations with odds ratios (*OR*s) approximately 1.3. The Exon 1 missense SNP rs13268757 displayed an average minor allele frequency of about 0.16 and about the same magnitude of *OR* (though with opposite phase of association) as that provided by the intronic SNPs. Power to detect these differences in these samples was 0.36 (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize).

There were trends, most with more modest magnitude, toward association in each of these same SNPs in the smaller sample of 79 lighter (<15 cigarette/day in both samples) smokers that provided low (0.1) power. Menthol preference was uniformly associated with 0.03–0.04 higher minor allele frequencies for these SNPs, providing *OR*s whose differences from unity were about ½ to ⅓ those found in heavier smokers. By contrast, the rs13268757 missense SNP provided about 0.7 *OR*s in both light and heavier smokers.

Table 1. *TRPA1* Single Nucleotide Polymorphisms (SNPs) Whose Allele Frequencies Provide Nominally Significant Differences Between Menthol-Preferring and Nonmenthol-Preferring European-American Heavy Smokers (≥15 cigarettes/day, n = 741)

					Heavy smokers					Light smokers				
SNP	bp	ex/intron	A1	A2	F_A	F_U	χ^2	*p* Value	*OR*	F_A	F_U	χ^2	*p* Value	*OR*
rs13268757	73150192	exon1	A	G	0.130	0.172	3.916	.048	0.719	0.104	0.140	0.372	.542	0.714
rs10111216	73149342	intron1	T	C	0.346	0.280	6.073	.014	1.362	0.360	0.333	0.101	.750	1.125
rs4738205	73146865	intron1	C	T	0.340	0.278	5.640	.018	1.340	0.360	0.333	0.106	.745	1.125
rs1373297	73144138	intron2	A	G	0.346	0.279	6.188	.013	1.366	0.360	0.333	0.101	.750	1.125
rs1443952	73143206	intron4	A	G	0.346	0.277	6.563	.010	1.379	0.360	0.333	0.101	.750	1.125
rs12677736	73139989	intron4	A	T	0.345	0.280	5.920	.015	1.357	0.360	0.333	0.101	.750	1.125
rs10101155	73134571	intron7	A	C	0.346	0.280	5.990	.014	1.359	0.360	0.337	0.076	.783	1.107
rs12548486	73134081	intron8	T	C	0.366	0.294	7.437	.006	1.390	0.360	0.333	0.106	.745	1.125
rs4737338	73124008	intron15	C	T	0.338	0.276	5.625	.018	1.340	0.360	0.324	0.200	.655	1.176
rs1373302	73120270	intron17	A	T	0.342	0.279	5.660	.017	1.341	0.360	0.330	0.134	.715	1.142
rs3824150	73104287	intron23	T	A	0.339	0.280	5.052	.025	1.318	0.360	0.324	0.200	.655	1.176

Note. Data from light (<15 cigarettes/day, $n = 79$) smokers added for comparison. Columns list: SNP identifier, basepair coordinates on chromosome 8 (build 36.3), ex/intron = position of nominally positive SNP in gene (introns assigned based on MapViewer annotation), A1 = minor allele (in European-Americans), and A2 = major allele. For heavy smokers: F_A = minor allele frequency in menthol-preferring subjects; F_U = minor allele frequency in subjects who prefer nonmentholated cigarettes, χ^2 = chi-squared test statistic for difference between minor allele frequencies in menthol- versus nonmenthol-preferring smokers, and p = statistical significance (not corrected for multiple comparisons). For light smokers: F_A = minor allele frequency in menthol-preferring subjects; F_U = minor allele frequency in subjects who prefer nonmentholated cigarettes, χ^2 = chi-squared test statistic for difference between minor allele frequencies in menthol- versus nonmenthol-preferring smokers, and p = statistical significance (not corrected for multiple comparisons). *OR* = odds ratio.

Discussion

Our present observations support biological bases for menthol preference in cigarettes that include common variations at the gene that encodes the *TRPA1* "menthol receptor." These data display several strengths: (a) the relatively large sample of European-American heavier smokers that provides *TRPA1* allele frequencies for menthol- and nonmenthol-preferring smokers, (b) information about brand preference was obtained by experienced interviewers and coded by raters blinded to genotype, (c) genotypes from Sequenom assays were confirmed by those from Affymetrix array assays in some of these samples (data not shown), (d) racial/ethnic self-identification was confirmed in other studies of some of these subjects by SNP results (Rose et al., 2010), (e) the results from the Duke and Molecular Neurobiology Branch/NIDA samples provide highly similar genetic association results (data not shown), and 6) the haplotype identified here is also a candidate to contribute to individual differences in effects of other substances that can act at *TRPA1*, including cannabinoids and chemical irritant/immobilizing agents (Bessac & Jordt, 2010; De Petrocellis et al., 2010).

Limitations of this work include (a) there is no classical genetic evidence that strongly supports genetic contributions to human menthol preference; this work thus provides some of the first evidence for biological bases for menthol preference. (b) The power of these samples was modest for the lighter smokers and moderate for the heavier smokers. (c) The *TRPA1* haplotype identified herein covers not only 5′ regions of this gene that contain the missense variant but also other regions of the gene. Variations throughout the *TRPA1* locus are thus candidates to contribute to the effects of the haplotype identified herein. (d) The 15 cigarette/day cutoff for separating heavier from lighter smokers appeared reasonable and allowed us to use the NIDA samples for which this was the only data available. Nevertheless, other cutoffs might be more appropriate for other samples that were assembled differently. After the samples described herein were genotyped, we studied a smaller sample of participants in an older treatment study that used somewhat different recruitment strategies and criteria (Rose et al., 2006). We identified significant associations with menthol preference for six *TRPA1* SNPs in smokers who smoked ≥20 cigarettes/day (rs3735943, rs3735945, rs920829, rs10104272, rs28546865, and rs10091803) but only one SNP that provided nominal significance when we used a 15 cigarette/day cutoff. (e) Although we focus on *TRPA1* here, variants in other TRP channels might also contribute to individual differences in menthol preference. In initial studies, we have identified more modest and variable association with several SNPs in the *TRPM8* gene that provides an additional menthol target, for example (GRU, DW JER, unpublished observations, July 30, 2010).

rs13268757 provides a nonconservative missense substitution of cystine for arginine in the first *TRPA1* exon. This missense SNP does appear to provide a functional *TRPA1* channel since the cystine that the minor allele encodes in humans is the amino acid at this position in the chimpanzee *TRPA1* sequence (http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=homologene&dopt=MultipleAlignment&list_uids=7189). This clear-cut change contrasts with the lack of compelling evidence for copy number variation or differential splicing in relation to the menthol preference–associated haplotype (http://projects.tcag.ca/variation/). Alterations in *TRPA1* based on the differences in its N terminal intracellular domain, its levels of expression, and/or regulation are thus all candidates to contribute to the menthol preference haplotype.

TRPA1 variations caused by this menthol preference *TRPA1* haplotype could contribute to some of the racial/ethnic differences observed in relative levels of use of mentholated cigarettes (Appleyard et al., 2001; Hooper et al., 2011; Lawrence et al., 2010; Osaki et al., 2006). dbSNP data documents frequencies of the 11 SNP alleles that form the menthol-associated "minor" alleles in European-American samples studied here that are all higher in Asian and African than in samples of European origin. In future studies, it will be interesting to seek association of this and other *TRPA1* haplotypes with menthol preference in smokers from these communities.

Preference for mentholated cigarettes may have significant consequences. The current data that provide significant support for biological bases for menthol preference due, at least in part, to variation at the genomic locus that encodes one of the key menthol "receptors" in the lung and airways also support roles for this menthol preference genetics in the greater nicotine dependence, poorer rates of smoking cessation, and interactions with race/ethnicity and socioeconomic status that have been identified in many, though not all, studies of menthol smokers (Gundersen, Delnevo, & Wackowski, 2009). If menthol allows disadvantaged smokers to extract more nicotine from each mentholated cigarette with fewer aversive symptoms, provides greater nicotine dependence for the same expenditures, and even leads to greater difficulty in quitting smoking (Gandhi, Foulds, Steinberg, Lu, & Williams, 2009; Gundersen et al., 2009), the haplotype that we report here could have a significant impact. In future studies, it will also be important to determine whether individuals with *TRPA1* variations smoke more in general, regardless of menthol preference. Identification of biological contributors to vulnerability to mentholated cigarettes could also help to inform current discussions about regulation of menthol in cigarettes (Mitka, 2009).

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Declaration of Interests

Duke University has submitted a patent application based on the menthol preference SNPs described herein. During the last three years, Dr. JER has received compensation from GlaxoSmithKline, Targacept, Catalyst Pharmaceutical Partners, Lorillard, Philip Morris USA, and Philip Morris International. Dr. JER and Ms. FMB have a spousal relationship. Dr. GRU, Ms. DW, and Ms. FMB have no other conflicts to disclose.

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