# REVIEW

# How Menthol Alters Tobacco-Smoking Behavior: A Biological Perspective

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Mentholated cigarettes gained popularity in the 1950s and were often marketed as "healthy" cigarettes, attributable to their pleasurable mint flavor and cooling sensation in the mouth, lungs, and throat. While it is clear that nicotine is the primary psychoactive component in tobacco cigarettes, recent work has suggested that menthol may also play a role in exacerbating smoking behavior, despite original health claims. Recent evidence highlights four distinct biological mechanisms that can alter smoking behavior: 1) menthol acts to reduce the initially aversive experiences associated with tobacco smoking; 2) menthol can serve as a highly reinforcing sensory cue when associated with nicotine and promote smoking behavior; 3) menthol's actions on nicotinic acetylcholine receptors may change the reinforcing value of nicotine; and 4) menthol can alter nicotine metabolism, thus increasing nicotine bioavailability. The purpose of this review is to highlight and evaluate potential biological mechanisms by which menthol can alter smoking behavior.

## I. INTRODUCTION

Tobacco cigarette use causes nearly 500,000 deaths annually in the United States, crowning it as the leading preventable cause of death [1]. Nicotine, a natural insecticide for the tobacco plant, is the primary psychoactive and addictive component in tobacco cigarettes. Nicotine addiction is largely characterized by a strong desire for nicotine, a buildup of sensitization for nicotine, withdrawal during abstinence, and a high likelihood of relapse during an attempt to quit. Notably, nicotine dependence is the most common form of chemical dependence in the United States [1]. One component thought to facilitate and exacerbate smoking behavior and ultimately lead to nicotine dependence, especially in adolescents, is added flavorants to smokable tobacco products. Perhaps surprisingly, even tobacco companies themselves have reported that flavors such as menthol can increase the appeal of smoking [2,3].

In an effort to stymie adolescent tobacco cigarette use, the Family Smoking Prevention and Tobacco Control Act (2009) banned adding flavors to tobacco cigarettes, with the exception of menthol. Such efforts are probably motivated by the frequent use of menthol in tobacco products. Specifically, mentholated cigarettes account for approximately 25 percent of all cigarette sales in the United States [4]. Moreover, more than 90 percent of all tobacco cigarettes contain menthol, regardless of being marketed as a mentholated cigarette. Thus, the range of menthol in a cigarette can range from imperceptible menthol (~0.03 percent of tobacco weight in "non-mentholated" cigarettes) to up to 0.1 to 1.0 percent in mentholated cigarettes [2,4]. As such, menthol is a pervasive component in tobacco products, and tobacco companies have a vested interest in the legal status of mentholated cigarettes.

Given menthol's widespread use in cigarettes, it is especially important to consider the behavioral differences between menthol smokers and non-menthol smokers. First, in adolescents, mentholated cigarettes are smoked at higher rates than non-mentholated cigarettes [5], indicating a preference for mentholated cigarettes during early tobacco use in adolescents. However, the age at which individuals begin smoking is similar for smokers of mentholated and non-mentholated smokers,

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suggesting that menthol does not lower the age at which individuals smoke but is preferred upon initiation of smoking [6]. Second, smokers of mentholated cigarettes have lower successful quit rates, despite having higher levels of quit attempts [7,8], which suggests that mentholated cigarettes may be more addicting than non-mentholated cigarettes. Third, mentholated cigarette smokers smoke their first cigarette of the day sooner than non-mentholated cigarette smokers [9], pointing toward a greater motivation to smoke mentholated cigarettes. Fourth, menthol cigarette smokers tend to smoke fewer cigarettes per day [10]. Since smokers (and other drug users) typically titrate their use to a preferred level of reinforcement, a decrease in number of cigarettes smoked indicates that the smoker requires fewer cigarettes to achieve the same level of reinforcement, which suggests that each individual mentholated cigarette is actually more reinforcing than a non-mentholated cigarette.

The profound effects of mentholation on smoking behavior suggest that menthol may be more than just a flavor added to cigarettes. Indeed, it recently has been shown that menthol has other biological effects that may explain how mentholation of tobacco cigarettes can promote nicotine dependence. Menthol has four biological mechanisms that likely contribute to altering smoking behavior. First, menthol's unique sensory properties mask the aversive properties of smoking tobacco cigarettes, such as unappealing taste and burning sensations in the throat and lungs. Second, these same sensory properties serve as cues that can serve as potent triggers of smoking craving and relapse. Third, menthol serves as a negative allosteric modulator of nicotinic acetylcholine receptors (nAChRs†), the principle site of action that mediates nicotine reinforcement. Fourth, evidence suggests that menthol can alter nicotine metabolism, increasing nicotine's bioavailability. This review will outline these four major biological mechanisms in the context of smoking behavior.

## II. MENTHOL BLUNTS THE AVERSIVE SENSORY EXPERIENCE OF SMOKING TOBACCO CIGARETTES

Recent publicly available data from tobacco company records strongly suggested the reason for including menthol as an additive was to minimize the aversive experiences associated with tobacco smoking and, thus, decrease smoking's perceived health risk [2,3]. These documents revealed that smokers of mentholated cigarettes report using them because they have less harsh, less irritating, and more soothing sensory profiles. Moreover, the flavor profile of mentholated cigarettes were reported to be improved compared to non-mentholated cigarettes, likely due to the appetitive minty flavor of menthol as well as its ability to mask aversive flavors of tobacco.

The mechanisms underlying menthol's multisensory actions are just beginning to become elucidated. Ingesting menthol lozenges or inhaling menthol vapor produces a cooling sensory experience in the mouth, throat, and airways leading to the lungs, which is mediated by menthol's actions on the cold-sensing Transient Receptor Potential Melastatin 8 (TRPM8) receptor expressed on sensory neurons [11]. Menthol's actions on TRPM8 receptors have been demonstrated to produce anti-irritant and analgesic properties in the lungs. Specifically, cigarette smoke-induced impairments in respiration in mice were reversed with aerosolized menthol [12]. It is important to clarify that these data are not suggesting that menthol prevents damage to the lungs but, rather, that menthol masks the sensation of irritation experienced by the smoker. Therefore, menthol's ability to counteract the irritating effects of tobacco smoke in the throat and lungs may explain the menthol preference in adolescents who may be more sensitive to the aversive experience of smoking. Indeed, mentholated cigarettes may produce less negative initial smoking experiences, thus making smoking more appealing. It is tempting to postulate that menthol smokers may then inhale cigarettes more deeply and, thus, absorb more nicotine, given menthol's anesthetic and anti-irritant properties. However, studies investigating this possibility have shown that mentholated smokers have similar puff frequency [13,14] and volume [14] to non-mentholated smokers. One important caveat is that these studies were all done in experienced smokers; thus, it is unclear how menthol may alter puff topography in adolescent or new smokers. One would predict that puff volume would be higher initially in new smokers using mentholated cigarettes compared to non-mentholated cigarettes due to menthol's anti-irritant and antitussive effects. Specifically, new smokers would be able to take deeper breaths with mentholated cigarettes, since there would be a reduction in lung irritation from smoking.

In addition to the anti-irritant and antitussive properties, menthol's flavor may mask the aversive flavor of tobacco cigarettes experienced by new smokers. (Experienced smokers likely do not find the flavor aversive.) Moreover, it recently has been reported that the presence of appetitive flavorants in electronic cigarettes are a major reason for adolescent experimentation with tobacco products [15]. Thus, menthol and other appetitive flavorants play a critical role in experimentation with tobacco cigarettes. Flavored tobacco products in general are preferred by young adults and adolescents and are often marketed toward them [16-18]. In response to the heavy marketing toward adolescents, the Family Smoking Prevention and Tobacco Control Act banned flavored cigarettes for the sole reason of reducing adolescent smoking. This legislation, however, does not regulate flavorants added to electronic cigarettes. Based on recent reports of electronic cigarette use in Connecticut, menthol and other appetitive flavors in electronic cigarettes probably promote adolescent smoking to a similar degree as traditional flavored tobacco cigarettes [15,19]. However, greater longitudinal data is needed to examine whether the flavored electronic cigarettes have a different addictive potential

than traditional flavored tobacco cigarettes. For menthol specifically, it is likely that both the flavor and sensory properties, such as cooling and anti-irritant and antitussive properties, contribute to adolescent use.

## III. MENTHOL AS A SENSORY CUE

As suggested in the previous section, the smoker's experience is not simply limited to acquiring nicotine from a cigarette. The same multisensory properties of menthol that can mask aversive properties of smoking also serve as potent environmental cues that promote smoking behaviors. Ultimately, menthol's sensory properties can double both as a masker of aversive experiences while smoking and as a sensory cue that has been associated with nicotine reinforcement. Specifically, the flavor of menthol or even the cooling of the lungs can serve as a distinct sensory cue outside of its masking properties, which can drive nicotine-taking behavior. Other environmental stimuli such as the location of smoking, the time of day and the motor action of bringing a cigarette to the lips to inhale also likely serve as environmental cues. The idea that environmental cues play a pivotal role in driving smoking behavior was derived by observing the relatively weak reinforcing properties of nicotine but paradoxically high rates of dependence. Indeed, rates of dependence for nicotine are at least comparable to other drugs of abuse such as heroin, cocaine, and amphetamines, yet the reinforcing properties of nicotine per se are considerably lower than these other drugs [20,21]. The difficulty of establishing nicotine self-administration in animal models compared to other drugs of abuse serves as a good example of the weak reinforcing properties of nicotine. Animal models of addiction utilize self-administration paradigms, which permit investigations into the neurobiological and behavioral processes that contribute to drug addiction and allow for the development of pharmacotherapies to prevent relapse and aid in cessation [22]. In intravenous self-administration paradigms, a rat is trained to press a lever (or some other operant behavior) for receipt of an intravenous delivery of a drug of abuse. Typically, rats will easily learn to press a lever for drugs such as cocaine, heroin, and amphetamine. However, rats have a more challenging time learning to lever press for nicotine [23]. Indeed, it is common in rat nicotine self-administration paradigms to require rats to first learn to press a lever for food before pressing that same lever for nicotine. The reason for requiring food training is likely because nicotine is initially aversive, and rats must be motivated to lever press for food (in extinction) to get through the aversive phase of nicotine self-administration [23,24]. More recently, nicotine self-administration without food training has been established in rat models [25]. One of the key advancements that obviates food training has been training rats to self-administer nicotine during their wake cycle (in darkness) instead of traditional methods that train rats during their sleep cycle (in the light). The requirement of these additional manipulations such as food training and day cycle training is typically absent from paradigms using other drugs of abuse. Therefore, it initially seemed paradoxical that nicotine dependence rates were similar to other more reinforcing drugs of abuse. This paradox has been largely resolved by the introduction of the dual-reinforcement model by Caggiula and colleagues [22]. Specifically, this model proposes that nicotine acts as both a primary reinforcer and as a reinforcement enhancer. The latter mechanism plays a critical role in promoting smoking behavior and, especially, in facilitating relapse.

The dual-reinforcement model suggests that smoking cues gain reinforcing value when nicotine is present, and these cues can serve to facilitate smoking behavior as well as relapse during abstinence. Typically, reinforcing value of a stimulus (i.e., cue, drug, or food) is assessed by how much an individual will work to obtain the stimulus. Thus, it will be assumed through the remainder of this discussion that a more rewarding stimulus will be more reinforcing than a less rewarding stimulus. Initially, a stimulus can be aversive, neutral, or rewarding. Once these stimuli are repeatedly paired with nicotine, the rewarding value for these stimuli increase. Initially aversive and neutral stimuli become rewarding, and initially rewarding stimuli become more rewarding. Thus, there is an increase in reinforcing value for stimuli associated with nicotine. For example, the burning sensation of tobacco smoke is initially aversive in new smokers. However, experienced smokers, who have had repeated pairings of nicotine and the burning sensation of tobacco smoke, often find the burning sensation reinforcing. Thus, an initially aversive sensory experience becomes reinforcing and has the potential to improve the smoker's experience. Further supporting the notion that smoking cues themselves are reinforcing, it has been shown that smoking cues are readily self-administered in humans [26]. Animal models also have demonstrated a similar effect of nicotine on enhancing the reinforcing properties of nicotine-associated cues. In rats, lever pressing for a naturally rewarding visual stimulus was greatly enhanced with either contingent or noncontingent presentations of nicotine, but not of sucrose [27,28]. Thus, nicotine can increase or enhance a stimulus' reinforcing ability and, in some cases, reverse an aversive stimulus to a reinforcing stimulus. For a menthol smoker, specifically, the mint flavor and the cooling sensation of the mouth, lungs, and throat serve as sensory cues whose reinforcing properties can be readily enhanced by nicotine.

A separate question that arose was whether the environmental stimuli could drive nicotine self-administration. This question was answered by a series of studies by Caggiula and colleagues examining the impact of environmental cues on acquisition and relapse of nicotine self-administration in rats [29,30]. In one study, rats were trained to self-administer nicotine either in the presence or absence of contingently paired cues. Rats that received paired cues with nicotine had a much more robust self-administration than rats that had no cue pairing with nicotine

[30]. In another study, rats were trained to lever press for nicotine while receiving a paired cue. Afterward, rats underwent extinction in which the lever press had no consequence — neither nicotine delivery nor cue presentation occurred upon lever pressing. Then, either the cue, nicotine, or both cue and nicotine were reintroduced to produce reinstatement of self-administration. Interestingly, the addition of the cues alone, and not nicotine alone, produced robust reinstatement of self-administration. The most robust self-administration was produced when both cues and nicotine were reintroduced. Thus, although nicotine itself may serve as a primary reinforcer, cues that have their reinforcing properties enhanced by nicotine may serve to promote smoking behavior and ultimately provoke relapse in abstinent individuals.

In the case of mentholated cigarettes, some of their multisensory properties are naturally rewarding, such as the mint flavor and cooling sensation. Indeed, smokers report that the flavor and sensory experience induced by menthol is pleasurable [2,3], although direct assessment of the reinforcing properties of menthol in humans is lacking. Nicotine may serve to increase menthol's reinforcing properties and permit menthol to sustain smoking behavior. In human menthol smokers, removing menthol from their cigarettes causes a drop in the subjective reward rating of the cigarette, despite similar levels of nicotine delivery [31]. These data suggest that menthol's cue properties may be facilitating the subjective liking of smoking. Similarly, animal models have also demonstrated that menthol's cue properties can facilitate nicotine-taking. In a paper by Wang at el., female rats that had an oral menthol cue paired with intravenous nicotine self-administration earned more nicotine infusions compared to oral vehicle cue with intravenous nicotine and had greater cue-induced (i.e., menthol-induced) reinstatement of nicotine self-administration [32]. Interestingly, menthol itself was self-administered at a lower rate than vehicle, suggesting that menthol's initial reinforcing properties are not major drivers of nicotine self-administration until after subsequent pairings with nicotine. Moreover, it was demonstrated that menthol's cooling properties, and not flavor, served as the primary cue mediating these effects [32]. These data strongly suggest that menthol's salient sensory properties serve as a nicotine-associated cue and may explain why menthol smokers have a harder time quitting than non-menthol smokers. It is likely that nicotine, through its reinforcement-enhancement ability, increases the reinforcing properties of menthol and further facilitates menthol's cue properties, especially cooling, to drive nicotine craving, taking, and relapse.

## IV. MENTHOL'S ACTIONS ON nAChRs IN MEDIATING NICOTINE REINFORCEMENT

While menthol has unique multisensory properties that can facilitate smoking behavior, menthol's actions on nAChRs are relatively poorly understood, likely due to the already complex mechanisms involving nAChRs, nicotine, and nicotine reinforcement. nAChRs are a heterogeneous family of pentameric, ionotropic receptors that are ubiquitously expressed in the nervous system [33]. nAChRs are comprised of five subunits, containing a mixture of α and β subunits. Typically, the junction between the α and β subunits is where both acetylcholine and nicotine bind [34], except for the case of homomeric α7 receptors, which lack β subunits [35]. Once activated, the channel becomes permeable to both Na+ and Ca2+. nAChRs are expressed on dendrites, cell bodies, and axon terminals and are able to modulate the release of virtually all neurotransmitters, especially dopamine (DA) [36].

DA neurons in the ventral tegmental area (VTA) exhibit two major modes of firing: tonic (~3-8 Hz in the rat) and burst (10-20 Hz in the rat) [37-40]. The transition from tonic to burst firing in DA neurons produces phasic, subsecond changes in DA release in the nucleus accumbens (NAc), which is important for mediating the reinforcing effects of natural and drug rewards [41-43]. Nicotine's euphoric properties are exerted through activation of nAChRs on neurons in the VTA, which produces large increases of DA in the NAc [41]. The α4β2* nAChR has been the most implicated in nicotine reinforcement, since its removal reduces DA neurons' sensitivity to nicotine, reduces nicotine-induced DA release in the NAc, and decreases nicotine self-administration in mice [44].

Nicotine reinforcement is also likely mediated by presynaptic α4β2* and α6β2* nAChRs located on DA terminals in the NAc. Basal levels of acetylcholine, arising from cholinergic interneurons, puts DA terminals in a higher probabilistic state of release compared to elevated levels of acetylcholine. When DA neurons are in tonic states of firing, presynaptic nAChR blockade with mecamylamine reduces phasic DA release [45-47]. However, when DA neurons burst-fire, nAChR blockade on DA terminals paradoxically enhances phasic DA release relative to control [45]. Nicotine, an agonist of nAChRs, has a similar effect on phasic DA release as nAChR antagonism [45,48]. This effect arises from the rapid desensitization of nAChR produced by nicotine. It is also unlikely that this phenomenon occurs at the level of the cell bodies in the VTA (where nicotine robustly induces burst-firing [49-51]), and desensitization of nAChRs in VTA does not appear to increase phasic DA release. In summary, activation of nAChRs on DA terminals reduces phasic DA release to DA neuron burst-firing, but phasic DA release is enhanced to DA neuron-burst firing either when these presynaptic nAChRs are desensitized or blocked. This mechanism has been though of as a "frequency-filter," permitting more exaggerated DA release to the different modes of DA neuron firing [46].

Only recently has the notion that menthol could directly interact with nAChRs arisen. Specifically, Hans and colleagues found that when menthol is bath-applied to trigeminal neurons, the ability of nicotine to depolarize these cells was reversibly reduced [52]. Moreover, when
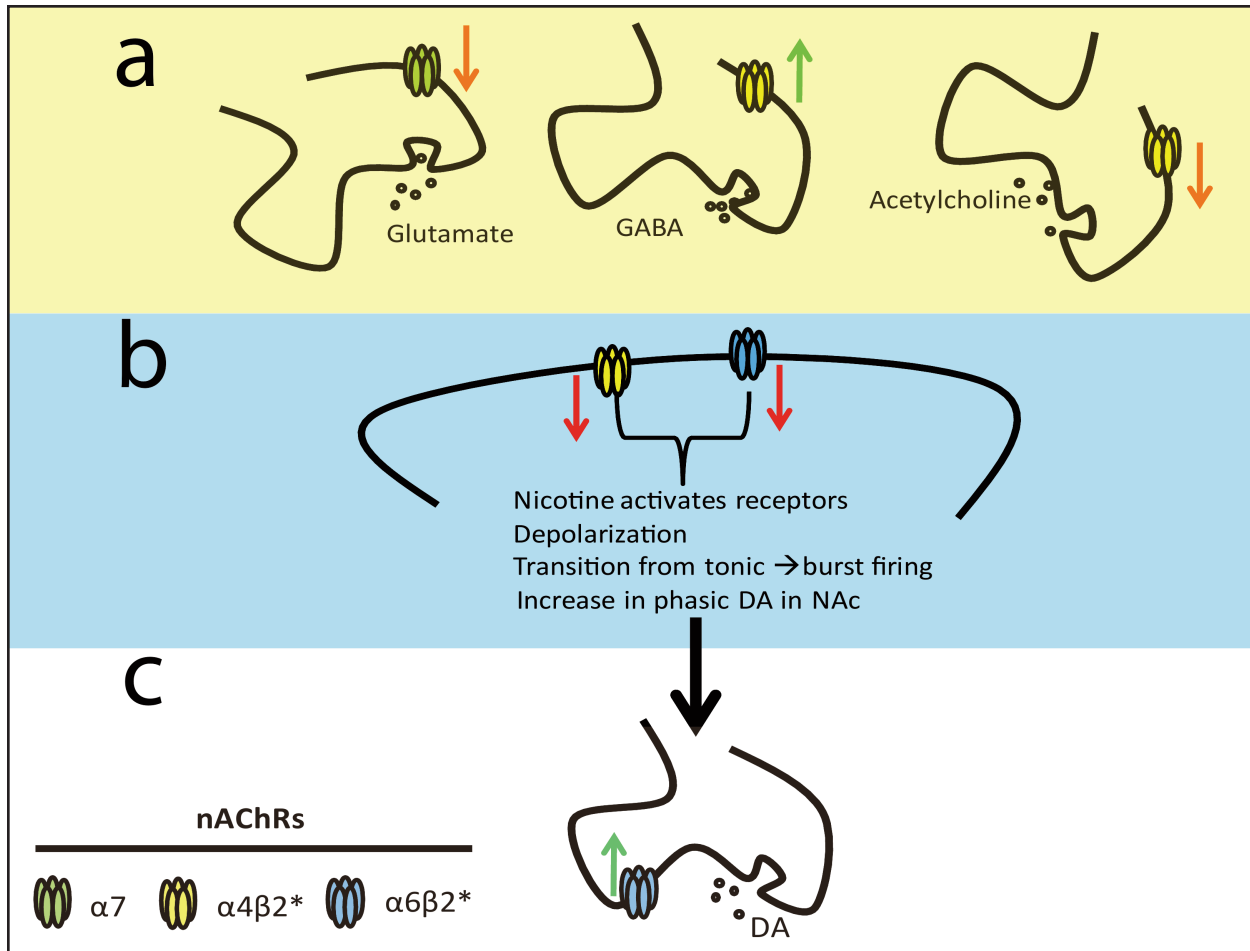
**Figure 1. Schematic how menthol can modulate phasic DA release in VTA and NAc. a) Presynaptic VTA nAChRs:** Presynaptic α7 nAChR are expressed predominately on glutamate terminals in the VTA. Menthol's actions here may be to reduce cholinergic and nicotinic activation of presynaptic α7 nAChRs, thus producing less glutamate and resulting in less burst-firing and phasic DA release [69]. Menthol acting on α4β2* nAChRs on GABA terminals may have the effect of decreasing inhibitory tone on DA neurons, relieving them from inhibition and increasing burst-firing and phasic DA release. In contrast, menthol acting on excitatory presynaptic α4β2* nAChRs on cholinergic terminals would decrease acetylcholine release elicited by nicotine and result in less burst-firing and phasic DA release. **b) Somatodendritic VTA nAChRs:** Somatodendritic expression of α4β2* and α6β2* nAChRs expressed on DA cell bodies may produce less burst-firing and subsequent phasic DA release to nicotine when menthol is present, since menthol decreases nicotine's efficacy at these receptors. **c) Presynaptic NAc nAChRs:** Menthol acting on presynaptic α6β2* nAChRs [70-72] located on DA terminals in the NAc would likely increase phasic DA release to DA neuron burst-firing, since menthol is effectively serving as an antagonist at this receptor.

the human α4β2* nAChR was expressed in HEK cells, menthol decreased the single channel current induced by nicotine. Acetylcholine activation of α4β2* nAChRs was not affected by menthol, indicating a nicotine-specific allosteric change in receptor function. In addition, α7 nAChRs appear to be inhibited by menthol; however, menthol inhibition of α7 nAChRs appears to be similar when activated by acetylcholine and nicotine [53], further confirming menthol's role as a negative allosteric modulator. Thus, menthol's actions on nAChRs may play a role in mediating nicotine reinforcement to mentholated cigarettes.

Menthol could have several actions on nAChRs located within the somatodendritic regions of the VTA and afferent terminals synapsing onto VTA dendrites (Figure 1). Acutely, if menthol is decreasing the current passing

through the channel pore of nAChRs, one would expect less activation of VTA DA neurons, less dopamine release in the NAc, and less reinforcement to nicotine. Alternatively, menthol may blunt nicotine's actions on β2* nAChRs on GABA neurons, which may lead to less inhibition of DA neurons, resulting in greater DA release. Additionally, menthol's actions on α7 nAChRs may be important. Blunting of nicotine's actions on the α7 nAChRs could result in less glutamatergic tone on VTA DA neurons, which would lead to less DA release.

An untested possibility is that menthol could stymie nAChR desensitization induced by nicotine, which may result in greater nicotine-induced phasic DA release. However, desensitization of nAChRs by nicotine is typically followed by upregulation of nAChRs [54,55], and a re-

| | Changing sensory experience | nAChR modulation | Slowing of nicotine metabolism | Cue properties |
|---|---|---|---|---|
| **Initial preference for mentholated cigarettes** | Reducing aversive effects of smoking, such as burning of lungs and coughing. | Increased euphoria due to greater dopamine release. | | |
| **Lower successful quit rates** | | Nicotine has greater reinforcement potential, thus making it more challenging to quit. | Greater addictive potential due to greater potency of each cigarette. | Menthol's multisensory properties serve as salient cues, which can drive nicotine-taking and make it harder to quit. |
| **Earlier first cigarette of the day** | | Greater motivation to smoke due to greater reinforcement of nicotine. | More motivation to smoke due to increased potency of each cigarette. | |
| **Smoke less cigarettes per day** | | Nicotine's increased reinforcing properties require less nicotine to achieve desired euphoria. | Greater nicotine bioavailaily would decrease the number of cigarettes smoked. | |

(The above table is captioned under the heading **MECHANISM** across the top and **SMOKING BEHAVIOR** down the left side.)

**Figure 2.** Potential biological mechanisms that can explain observed smoking behavior differences between menthol and non-menthol smokers.

cent report suggests that menthol smokers have increased expression of nAChRs in prefrontal cortex and other brain regions [56], although the VTA and NAc were not examined. These data would suggest that nicotine's ability to induce nAChR desensitization is similar or stronger in mentholated versus non-mentholated cigarettes. However, menthol could upregulate nAChRs through mechanisms outside those that involve nAChR desensitization.

Another important mechanism for regulating nicotine's reinforcing properties may be menthol's effect on presynaptic nAChRs located on DA terminals in the NAc (Figure 1). At least initially, nicotine would activate presynaptic DA terminals via presynaptic nAChRs, causing a decrease in phasic DA release during burst-firing. Then, after desensitization, phasic DA release would increase. If menthol blunts nicotine's actions on presynaptic nAChRs without altering desensitization, then one would expect a greater overall phasic DA release profile by blunting nicotine's initial activation of presynaptic α4β2* and α6β2* nAChRs.

Taken together, this evidence suggests it is likely that menthol has some action on nicotine-induced phasic DA and, thus, nicotine reinforcement. Menthol's actions on nAChRs have the potential to increase the overall reinforcing value of nicotine and, by proxy, tobacco cigarettes. Thus, these effects would then explain why menthol smokers have increased desire to smoke upon waking. If

each cigarette has a more reinforcing value due to menthol enhancing phasic DA release, then one would expect menthol smokers to be more motivated to smoke and to therefore smoke the first cigarette of the day earlier. Moreover, the finding that menthol smokers smoke fewer cigarettes per day would be consistent with greater nicotine reinforcement in that fewer cigarettes would be required to reach the same level of desired reinforcement. Indeed, if menthol enhances phasic DA release to each cigarette, then the smoker would titrate downward the number of cigarettes smoked. Finally, in concert with greater motivation to smoke and increased reinforcing value of each cigarette, it is consistent then through menthol's actions on nAChRs that cessation outcomes would be worse; it is assumedly harder to quit a drug one is more motivated to take and gets greater pleasure from taking. However, experiments that directly address how menthol alters phasic DA release to nicotine and nicotine reinforcement are warranted in order to draw any strong conclusions.

## V. MENTHOL'S ACTIONS ON NICOTINE METABOLISM

Perhaps the most well-studied effect of menthol in relation to tobacco smoking is menthol's ability to alter nicotine metabolism. Indeed, individual differences in nicotine

metabolism have been shown to be the strongest predictor of nicotine dependence and cessation success [57-59]. Specifically, greater dependence and poorer cessation outcomes are well-predicted by faster metabolism of nicotine [57,58]. Nicotine is metabolized by the cytochrome protein 2A6 (CYP2A6) into cotinine, which is metabolized by the same enzyme into trans-3'-hydroxycotinine (3HC) [60,61]. Additionally, in the case of inhaled tobacco products (e.g., cigarettes), nicotine escapes hepatic and intestinal first-pass metabolism, which can help contribute to more rapid and complete absorption into the blood stream and, ultimately, more rapid reinforcement [60]. Typically, individuals with faster nicotine metabolism will have a harder time quitting, and individuals with slower nicotine metabolism will have better cessation outcomes [57]. Asians and Blacks metabolize nicotine more slowly into cotinine than Hispanics or Whites, while women metabolize nicotine faster than men [60,62-64]. Since Blacks predominately smoke menthol cigarettes (~75 percent preferences) compared to Whites (5 to 20 percent), it was examined whether menthol could account for the slower metabolism in Blacks by interfering with nicotine metabolism [65,66]. Pérez-Stable and colleagues investigated smoking differences between Blacks and Whites and found that Blacks had more nicotine intake per cigarette and higher plasma cotinine levels per cigarette, indicating lower CYP2A6 activity [66]. A later study controlling for race demonstrated that smoking mentholated cigarettes decreased the metabolic clearance of nicotine, through inhibiting CYP2A6 activity, but did not alter nicotine intake [67]. Taken together, both race and presence of menthol each contribute to differences in nicotine metabolism, potentially increasing the bioavailability of nicotine in the body.

On one hand, nicotine metabolism is slower, which should then predict lower dependence scores and better cessation outcomes. Thus, it is surprising that menthol smokers have poorer cessation outcomes. On the other hand, if nicotine were more bioavailable, then more nicotine would be able to reach the brain, potentially enhancing the cigarettes' reinforcing value. If this were to be true, then this mechanism could explain why menthol smokers smoke fewer cigarettes per day, since fewer cigarettes are needed to achieve the desired concentrations in the brain. However, in opposition to this proposed mechanism, adolescents with slower nicotine metabolism actually smoke more cigarettes per day and exhibit higher nicotine dependence [62,68]. Thus, it is likely that menthol has additional actions (Sections II, III, and IV) on nicotine reinforcement and dependence outside of inhibiting nicotine metabolism.

## VI. CONCLUSIONS AND IMPLICATIONS

Menthol is not simply a flavor, despite being heavily marketed as such, but acts through several mechanisms that all can contribute to greater nicotine use and eventual dependency (Figure 2). Menthol's cooling, antitussive, anti-irritant, and anesthetic properties likely reduce the initial aversive experience of tobacco smoke in new smokers. Interestingly, menthol was the only flavor excluded from the Family Smoking Prevention and Tobacco Control Act. The purpose of this act was to discourage smoking in adolescents by restricting their access to appetitive chocolate and candy tobacco cigarette flavors. However, this act only considered the flavor component of additives. Indeed, a more detailed consideration of menthol's multisensory properties beyond flavor is warranted. This is especially true in light of the finding that nicotine enhances the reinforcing properties of naturally reinforcing stimuli. Menthol and other flavors that are intrinsically appetitive may be sustaining and enhancing tobacco use through mechanisms other than the flavor, per se. Rather, nicotine may be enhancing their reinforcing value to a degree beyond the appetitive value of their flavor. Moreover, these flavors are then serving as potent cues, which can drive further smoking behavior. Another important consideration outside of menthol's flavor is its ability to modify nAChR sensitivity to nicotine via negative allosteric modulation. Although more studies need to be done to examine menthol's effects on DA release and nicotine reinforcement, it is likely that menthol is altering nicotine's effects on the DA system (Figure 1).

Menthol's interaction with nicotine addiction may have critical policy and regulatory implications. If regulatory agencies decide, for example, to limit the amount of nicotine in tobacco products to sub-addictive levels, then this approach may not be feasible for mentholated nicotine's increased reinforcing properties and enhanced nicotine bioavailability, which would effectively take a sub-addictive dose of nicotine and make it addictive. In addition to menthol's effect on nicotine reinforcement and bioavailability, it is unknown how menthol interacts with common tobacco cessation strategies. Nicotine pharmacotherapies such as varenicline, which have agonism at α7 nAChRs and partial agonism at α4β2* nAChRs, may be differentially effective in menthol smokers due to menthol's allosteric actions. No known study to date has investigated this possibility in individualized treatment of nicotine dependence. Future research should be directed at examining how menthol alters nicotine's reinforcing properties and the neural mechanisms underlying them, which would have significant implications for the treatment of nicotine addiction.

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