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Authors

Lallai, Valeria
Fowler, Christie D

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Commentary

More Than Just Chillin': Interactive Effects of Menthol and Nicotine in Drug Reward

Valeria Lallai¹ and Christie D Fowler^{*,1}¹Department of Neurobiology and Behavior, University of California Irvine, Irvine, CA, USA

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'...it appears that nicotine and menthol combine in an additive manner to determine degree of impact' -Philip Morris Internal Memo, Gullota *et al* (1989)

Menthol is a common additive found in varying concentrations in most tobacco cigarettes, as well as a flavorant in electronic vapor cigarettes (e-cigarettes). The impact of flavorants in promoting initial use and later dependence has been a concern since shortly after their introduction into the marketplace. Indeed, the potential for menthol to interact with nicotine and thus promote dependence was noted by the cigarette industry over 25 years ago, with subsequent product development efforts focused on exploiting this interaction to increase user consumption (Gullota *et al*, 1989). More recently, population-based studies have established that a large proportion of youth preferentially consume flavored tobacco products, with estimates as high as 80% (Villanti *et al*, 2017). Moreover, adult women and racial/ethnic minorities, including African Americans, Latinos, and Pacific Islanders, disproportionately consume mentholated nicotine products (FDA, 2013; Villanti *et al*, 2017). While this increased consumption by some populations has been proposed to be due to focused marketing in targeted communities, genetic/biological factors (eg, differences in drug metabolism or receptor expression) may also underlie an increased vulnerability for dependence.

Traditionally, menthol has been considered non-harmful based on its common use in a variety of consumer products (lip balm, cough medication, topical analgesic, mouthwash, and food flavorant) and relatively non-toxic effects (FDA, 2013). Menthol's characteristic cooling sensation has been attributed to increased Ca²⁺ influx through activation of the TRPM8 thermoreceptor, a mechanism that has been proposed to counteract the aversive oral properties of nicotine and thus promote palatability and consumption

(Fan *et al*, 2016). However, emerging evidence has led to a reassessment of the impact of menthol on addiction processes in consideration of the documented central effects on cholinergic signaling mechanisms. For instance, chronic menthol treatment, in the absence of nicotine, has been shown to induce an upregulation in nicotinic acetylcholine receptors (nAChRs) in GABAergic midbrain neurons and to alter the stoichiometry of subunit expression by stabilizing lower sensitivity receptor subtypes (Henderson *et al*, 2016).

In this issue of *Neuropsychopharmacology*, Henderson *et al* (2017) provide evidence to support the hypothesis that menthol and nicotine act synergistically to upregulate nAChR expression in dopaminergic neurons; effects that are proposed to mediate a functional enhancement in neuronal excitability. These findings represent a significant advance in our understanding of how both nicotine and menthol may act together to mediate nicotine addiction. In these studies, menthol and nicotine co-administration induced a conditioned place preference (CPP) for a subthreshold dose of nicotine and potentiated CPP expression for a rewarding dose of the drug. However, administration of menthol alone did not result in the development of a CPP. Thus, these data suggest that nicotine and menthol interact synergistically to drive reward-related behaviors. It is worthwhile to note that in their prior study, chronic treatment with menthol alone prevented the formation of a CPP for nicotine (Henderson *et al*, 2016). While these data may initially seem contradictory, the duration of exposure and pharmacokinetics associated with acute co-administration likely mediated the differential reward-related effects. In the prior study, menthol was administered continuously in a minipump for 11 days and during CPP training. Thus, the continuous baseline level of menthol exposure may have altered circuit responsivity during both the nicotine and vehicle training sessions. In contrast, the current study co-administered nicotine and menthol acutely during CPP training (Henderson *et al*, 2017), thus providing a more accurate assessment of co-exposure similar to that found with nicotine product consumption in humans. Another strength of the current study is reflected by the fact that the authors have taken into account both the ratio of menthol to nicotine in a typical mentholated cigarette and

*Correspondence: Dr CD Fowler, Department of Neurobiology and Behavior, University of California Irvine, 1232 McGaugh Hall, Irvine, CA 92697, USA, Tel: +1 949 824 8363, Fax: +1 949 824 2447, E-mail: cdfowler@uci.edu

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respective brain penetration levels. Given these important considerations, the current approach offers a rationale foundation by which the findings support translational relevance to human smokers. Finally, since both menthol and nicotine were administered peripherally, rather than orally, the rewarding properties cannot be attributed to the buccal effects of either substance in the current study, thus providing a distinct advantage when attempting to disentangle sensory *vs* central effects of menthol and nicotine action.

In consideration of the potential effects of menthol on other receptor mechanisms, such as TRPM8, the authors extended their investigations to demonstrate the direct effects of menthol and nicotine on nAChRs in dopaminergic neurons. In these studies, midbrain cultures from tyrosine hydroxylase-eGFP mice were examined to assess electrophysiological changes in dopaminergic neuronal activity. Chronic treatment with menthol and nicotine decreased baseline firing frequency, and following acetylcholine application, neuronal firing frequency increased to levels greater than that found with chronic nicotine treatment alone. Thus, the authors hypothesized that differential nAChR expression may underlie the documented alterations in cellular activity. Indeed, receptor upregulation paralleled the differences found in neuronal excitability. Specifically, while chronic nicotine increased $\alpha 4$ - and $\alpha 6$ -containing nAChRs in both the ventral tegmental area and substantia nigra, menthol and nicotine together induced greater upregulation of $\alpha 4$ -containing nAChRs in these regions. Pixel-based FRET further confirmed these findings to support the conclusion that menthol and nicotine co-treatment results in greater expression of $\alpha 4\alpha 6$ -containing nAChRs in the ventral tegmental area.

In sum, these findings emphasize the importance of determining the impact of flavorants and other constituents in tobacco/nicotine products on addiction-related processes. Additional research will be necessary to delineate the interactive effects of nicotine and menthol on the balance of dopaminergic and GABAergic circuit function *in vivo*, as well as their effects on the neurobiological mechanisms mediating various aspects of dependence, such as reinforcement, withdrawal, and relapse. As the current study provides

direct evidence that nicotine and menthol interact on a cellular level to modulate cholinergic signaling mechanisms (Henderson *et al*, 2017), this interaction may contribute to the disproportionate use and dependence found in certain populations. As such, future policy approaches should take into account the effects of product constituents in the regulation of product availability and marketing to vulnerable populations.

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