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Addiction Research

Menthol Precipitates Nicotine Intake in Young Subjects

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ABSTRACT

Community survey studies have shown that adolescents and young adults start to experiment smoking with menthol cigarettes. However, the issue of how menthol prompts the acquisition of nicotine consumption and facilitates progression to addictive smoking has received little experimental attention due to ethical concerns. In this report, we used a rat model of nicotine addiction to demonstrate an enhancing effect of menthol on nicotine consumption. Specifically, menthol-treated adolescent rats, compared their control counterparts, learnt significantly faster lever press responses for nicotine self-administration. Menthol pretreatment further enhanced nicotine self-administration under a higher response demand. These findings present empirical evidence for menthol's role in the start and development of tobacco addiction.

Keywords

Menthol, Nicotine, Adolescent.

In spite of the fact that the great efforts over the past several decades have led to the overall reduction of tobacco smoking, the use of mentholated tobacco products appears to be an alarmingly growing problem, in particular among the younger population [1]. Increasing epidemiological surveys and clinical observations have shown a significant impact of mentholated tobacco products on perpetuation of tobacco use [2-10]. However, the issue of whether menthol facilitates the initiation and progression of smoking behavior has never directly been examined in human subjects due to ethical reason. Unfortunately, even in animal research field this issue has not yet received adequate experimental attention. Our laboratory, using animal models of nicotine addiction, investigated whether and how menthol influences the acquisition and progression of nicotine self-administration in adolescent subjects. Specifically, a nicotine self-administration paradigm was used for examining effects of menthol on the acquisition of nicotine-taking behavior and progression to stable nicotine intake under high behavioral demands.

This study used male Sprague-Dawley rats with an indwelling intravenous catheter inserted in the right external jugular vein. Starting at adolescent age (postnatal days 48-59), rats were tested for lever-pressing responses to self-administer nicotine at 15 µg/kg/injection in daily 1-h sessions. To examine the effect of menthol on acquisition of nicotine-taking behavior, five min prior to the seven daily test sessions, different groups of rats were subjected to an intraperitoneal administration of menthol at doses of 0 (vehicle), 0.75 or 2.5 mg/kg. The selection of menthol doses was based on our previous work showing that menthol at 2.5 mg/k/g significantly enhanced nicotine reinforcement [11]. In these sessions, animals were rewarded for each lever-pressing response (i.e., fixed-ratio 1 schedule) with an intravenous nicotine injection. In separate groups of rats, the effect of menthol on progression of nicotine-taking behavior was examined. After animals had learnt lever-pressing for nicotine self-administration, the progression of nicotine intake under an elevated behavioral demand, i.e., a fixed-ratio 5 schedule was tested across five daily sessions. Similar to what happened in the acquisition tests, five min prior to the progression test sessions, rats were subjected to an intraperitoneal administration of menthol at 0 (vehicle), 0.75, and 2.5 mg/kg.

As compared to the animals in the vehicle-treated group, the rats pretreated with menthol at 2.5 mg/kg emitted significantly more lever-pressing responses to self-administer nicotine across the seven test sessions. As such, these animals earned significantly more intravenous injections of nicotine. Furthermore, in the animals that had already learnt nicotine self-administration behavior, pretreatment with menthol at 2.5 mg/kg facilitated their responses under a higher behavioral demand, i.e., fixed-ratio 5 schedule. This

effect was observed in the last three sessions across the five testing days. However, it should be noted that in all these test sessions, menthol did not change animals' lever-pressing responses emitted on an inactive lever. Since no reward was delivered after inactive lever responses, it is thought of as a reference indicting the state of general arousal and locomotor activities. Therefore, the observed behavior-enhancing effect of menthol was specific for nicotine-taking behavior.

These findings demonstrated that menthol facilitated these adolescent rats to lever-press for nicotine self-administration, indicating that menthol promoted the acquisition of nicotine-taking behavior. The result that menthol further made animals increase their lever-pressing responses under a higher behavioral demanding condition, i.e., from a fixed-ratio 1 to a fixed-ratio 5 schedule, indicates the facilitating effect of menthol on the progression of nicotine-taking behavior.

These laboratory research results present support for clinical observations suggesting that menthol cigarettes might promote smoking experimentation and initiation in adolescents and young adults [12]. Our results are in line with other animal studies relevant to menthol effect on nicotine actions in young subjects. Adolescent rats pretreated with menthol showed an enhanced nicotine-induced locomotor sensitization as measured in an open field test. In these animals, menthol significantly increased functional connectivity monitored using functional magnetic resonant imaging scan in brain regions involved in rewarding and addiction process such as ventral tegmental area and striatum [13,14]. In adolescent smokers, menthol significantly enhanced the positive reinforcing effects of nicotine in e-cigarettes so that menthol e-cigarette users showed higher levels of liking and wanting of the menthol-containing e-cigarettes compared to the ones without menthol content [7,10]. After increasing the cost for obtaining nicotine self-administration via change the fixed-ratio schedule from 1 to 5, rats pretreated with menthol relative to vehicle controls showed a quicker increase in their lever-pressing responses. Correspondingly, these animals self-administered a higher level of nicotine compared to vehicle counterparts. These findings match with clinical observations showing the heightened progression of menthol smokers. In USA, young people who start smoking menthol cigarettes are at greater risk of progression to regular smoking and nicotine dependence than their counterparts starting smoking with non-menthol cigarettes [12]. In a similar community survey study conducted in Canada, high school students (9-12 grades) who smoked menthol cigarettes not only consumed more cigarettes but also showed stronger intention to continue smoking compared with nonmenthol counterparts [15].

In conclusion, increasing human epidemiological and clinical observations suggest that menthol might interact with nicotine to promote tobacco use. The present study provides empirical evidence to support such an assumption. The findings from this study demonstrate the facilitative effect of menthol on the initiation and progression of nicotine-taking behavior in adolescent subjects. These results help our understanding of the fact that addiction of menthol in tobacco products do promote smoking behavior in young population. It warrants a ban for addition of menthol in tobacco products.

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