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Addiction Research

Menthol Facilitation of Nicotine Intake Evidenced Using Animal Models of Tobacco Addiction

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Tobacco, Menthol, Addiction.

Menthol is a monocyclic terpene alcohol that exists in plants of the Mentha genus. It is commonly known as mint. Menthol is a significant flavoring additive in tobacco products. Menthol-labeled cigarettes account for approximately one third of the total tobacco market. As a matter of fact, almost all commercial tobacco products, even though not menthol-labeled, contain a certain amount of menthol. In the United States, relative to the overall significant progress in reducing tobacco smoking over the past several decades, the increasing consumption of mentholated tobacco products has become a growing problem [1-3]. Particularly alarming is that adolescents have shown a greater preference for mentholated tobacco products when they engage in experimenting with tobacco use [4,5].

Clinical observations suggest a significant impact of menthol on perpetuation of tobacco epidemic from increasing experimentation with smoking to decreasing smoking cessation success [1,6-11]. In adolescents and young adults, majority of smokers started their smoking with mentholated tobacco products. Although almost all smokers want to quit smoking and have made attempts to do so, the majority eventually relapses and continues to smoke. Menthol cigarette smokers relative to nonmenthol users usually show less success of smoking cessation and higher rates of relapse.

Our recent laboratory research using animal models of nicotine consumption and relapse has shown empirical evidence for a significant role of menthol in facilitating tobacco addiction. Male Sprague-Dawley rats were trained in daily 1-h sessions to press a lever for intravenously self-administering nicotine under a fixed-ratio 5 schedule of reinforcement. Five minutes prior to the test sessions, menthol was administered. The results showed that menthol pretreatment shifted the nicotine dose-response curve to the left, indicating an enhancing effect of menthol on nicotine reinforcement. In a different set of rats that self-administered 0.015 mg/kg/infusion nicotine, a dose on the ascending limb of the dose-response curve, the facilitating effect of menthol on nicotine self-administration was dose-dependent with doses at or higher than 2.5 mg/kg producing its enhancing effect, whereas, doses at or lower than 1 mg/kg being ineffective. Interestingly, menthol at doses above the threshold of 2.5 mg/kg showed a similar magnitude of its effects. Moreover, using a progressive-ratio schedule of reinforcement that measures the strength of nicotine reinforcing actions and rats' motivation for obtaining nicotine reward, pretreatment with 2.5 mg/kg menthol significantly increased the maximum number of lever responses that rats willingly made to earn the intravenous nicotine injections. Thus, these data suggest that menthol directly strengthens the rewarding effects of nicotine and thereby promotes nicotine consumption [12].

In addition to the direct enhancing effect on nicotine reinforcement, menthol can create an unique internal state for smoking and nicotine intake and thus acquire the properties of interoceptive cues for tobacco use. It is hypothesized that menthol may become an occasion-setter that is predictive of the presence of nicotine reinforcement and thereby sustains smoking. This hypothesis was tested using a rat model of nicotine-seeking behavior. Briefly, rats were trained to self-administer nicotine and a nicotine-conditioned cue was established via associating presentation of a visual/auditory stimulus with each nicotine delivery. Prior to these sessions, rats received an administration of menthol so that the self-administration of nicotine happened in a menthol-produced internal state. Then, the perseverance of nicotine-seeking behavior was examined without nicotine availability. Results showed that continued pre-session menthol administration or in-session cue presentation sustained the lever-press responses on the previously

nicotine-reinforced (active) lever, indicating that these two factors individually lead to the perseverance of nicotine-seeking behavior. Moreover, combination of continued menthol administration and cue presentation resulted in a much higher level of lever responses relative to either alone, indicating that menthol interacted with the cue to produce a more robust behavioral motivational effect. These data indicate that continued exposure to menthol or nicotine-conditioned cues, and particularly their combination significantly sustained nicotine-seeking behavior [13].

In a separate set of rats, effect of menthol on relapse to nicotine-seeking behavior was determined. Specifically, after establishment of nicotine self-administration with pre-session menthol administration, rats were subjected to extinction training where nicotine availability, pre-session menthol administration and in-session cue presentation were withheld. The relapse tests were performed after responses were extinguished. In the test sessions, re-administration of menthol or re-presentation of nicotine cue effectively reinstated lever-press responses on the active lever, indicating relapse of nicotine-seeking behavior. More significantly, the magnitude of reinstatement of lever responses by the combination of menthol and cue was larger than that induced by either alone, indicating a much stronger relapse-triggering effect [13].

In conclusion, menthol can acquire occasion-setting properties and thus set an internal state for nicotine self-administration. The menthol-produced interoceptive state (an occasion setter) signaled the availability of nicotine reward and brought the rats into contact with the lever. The response-contingent presentation of nicotine cues then served as conditioned reinforcer to support responding on the lever. Therefore, in the extinction tests, the continued presence of menthol sustained nicotine-seeking responses relative to the menthol omission counterparts. And in the relapse tests, menthol re-administration effectively reinstated nicotine-seeking responses. In particular, such an interoceptive cueing effect of menthol interacted with nicotine-conditioned environmental cues to produce a more robust motivational effect.

These findings may have clinical implications. First, menthol can strengthen the rewarding effects of nicotine and thereby promotes nicotine consumption. Second, abstinent smokers who used mentholated tobacco products may experience stronger craving for tobacco when they ingest menthol-containing products, such as chewing gum or drinking minty drinks. Thus, refraining from exposure to all menthol-containing products during smoking cessation is expected to protect individuals from strong tobacco craving. And in particular important, these abstinent smokers should also avoid exposure to environmental stimuli previously associated with smoking.

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