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**Menthol enhances the addiction to nicotine**

In recent years, there has been a convergence of preclinical and clinical science that supports the understanding that the chemical flavorant, menthol, promotes and enhances dependence upon nicotine. Nicotine, has been considered the primary addictive component of all tobacco and e-cigarette products (1, 2). Before, discussing how menthol specifically alters the brain to promote dependence we need to first outline the details of nicotine's actions.

The common mechanism among all drugs that trigger dependence is that they all alter dopamine neurons and the release of dopamine in key brain areas, such as the nucleus accumbens. Nicotine binds the proteins called nicotinic acetylcholine receptors. Henceforth, I will just refer to them as nicotinic receptors. For many years, there has been a long-established body of science that the number of nicotinic receptors increases in the brain (termed upregulation) due to long-term exposure to nicotine. This has been observed in humans, animal models, and cultured cell models (3-6). One brain area that exhibits robust nicotine-induced nicotinic receptor upregulation is the ventral tegmental area (5). In this region, there are dense populations of dopamine neurons and nicotine-induced upregulation of nicotinic receptors results in a change in brain circuit mechanisms that depresses dopamine neuron activity (and dopamine release) when nicotine is absent (7, 8); but promotes enhanced dopamine release when nicotine is present (9, 10). This presumably accounts for the nicotine-seeking (during dopamine deficits) and nicotine reinforcement (during elevated dopamine).

Several of the key events that are caused in the brain by nicotine have been shown to be enhanced by menthol. First, there was an observed enhancement in nicotinic receptor upregulation in the brains of human menthol smokers when compared to smokers of unflavored cigarettes (11). This has been repeated in an animal model and here it was determined that not only was this increase in nicotinic receptors responsible for an enhancement in nicotine addiction-related behavior; but it was demonstrated that dopamine neuron excitability is enhanced by menthol plus nicotine when compared to nicotine alone (12). As a reminder, dopamine neurons are critical for addiction-related behavior. Therefore, the ability of menthol to increase their excitability compared to nicotine-alone suggests that menthol increases the ability of nicotine to alter neurons that are key for encoding dependence to nicotine. In preclinical models of addiction-related behaviors, multiple research groups have determined that menthol will enhance the self-administration of nicotine (13-15). Drug self-administration is the gold-standard for preclinical models to increase our understanding of all drugs of dependence. Hence, the findings of multiple independent labs that menthol will increase the self-administered intake of nicotine support the foundation that menthol enhances addiction-related behaviors to nicotine.

This of course is complemented by the observations of human smoking populations. Smokers of menthol cigarettes exhibit lower cessation rates (16-18). This is likely due to the fact that smokers of menthol cigarettes perceive menthol-containing products to be more pleasurable or rewarding (19). These reports are supported by other prior published scientific studies that observe several metrics: 1) menthol increases puff duration; menthol increases number of cigarettes smoked per day; menthol facilitates initiation of smoking behaviors; and menthol decreases time to first cigarette per day (19-21). Overall, there is agreement in both preclinical and clinical research models: menthol likely enhances the addiction to nicotine.

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