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Menthol facilitates dopamine-releasing effect of nicotine in rat nucleus accumbens

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ABSTRACT

Menthol is a significant flavoring additive in tobacco products. Accumulating clinical evidence suggests that menthol may promote tobacco smoking and nicotine dependence. Our previous studies demonstrated that menthol enhanced nicotine reinforcement in rats. However, it is unclear whether menthol interacts with nicotine at the neurochemical level. The present study used intracranial microdialysis to examine whether and the ways in which menthol affects nicotine-induced dopamine release in rats in the nucleus accumbens core (NAc), a terminal field of brain reward circuitry. To make comparisons with our previous work that showed an enhancing effect of menthol on nicotine self-administration behavior, male Sprague-Dawley rats were first trained in 20 daily 1-h sessions to press a lever for intravenous nicotine self-administration (15 μg/kg/infusion). Dopamine levels were then measured in the right NAc using intracranial microdialysis coupled with high-performance liquid chromatography. Five minutes before microdialysis, the rats received an intraperitoneal injection of menthol (0, 1, 2.5, and 5 mg/kg), a subcutaneous injection of nicotine (0.2 mg/kg or its vehicle), or both. Menthol alone did not affect dopamine levels in dialysates, whereas nicotine alone elevated dopamine levels. Combined nicotine and menthol administration significantly increased dopamine levels compared with nicotine alone. These data indicate a facilitating effect of menthol on nicotine-induced dopamine release in the NAc. These findings shed light on our understanding of the neurobiological mechanisms that underlie the menthol-induced enhancement of nicotine reinforcement.

1. Introduction

In the United States, approximately 40 million adults are current smokers (CDC, 2015), and approximately one-third of these smokers use menthol cigarettes (Caraballo and Asman, 2011; Curtin et al., 2014; Pearson et al., 2012; SAMHSA, 2009). Relative to the overall significant progress in reducing tobacco smoking over the past half century, the use of mentholated cigarettes, particularly among the younger population, has become a growing concern (Giovino et al., 2015; SAMHSA, 2009; USDHHS, 2014).

Accumulating clinical and epidemiological studies have reported the significant impact of menthol on tobacco smoking and addiction. Such an impact manifests as higher rates of smoking experimentation and progression to regular smoking and lower rates of smoking cessation success (Anderson, 2011a, 2011b; Benowitz and Samet, 2011; Delnevo et al., 2011; Delnevo et al., 2015; Fagan et al., 2015; Giovino et al., 2015; Tobacco, 2011; TPSAC, 2011). For example, evidence indicates that menthol smokers have a shorter latency to smoke their first cigarette in the morning after waking up, inhale more deeply, and have higher levels of nicotine addiction (Ahijevych and Parsley, 1999; Hoffman and Simmons, 2011; Muscat et al., 2009; Okuyemi et al., 2003; Richter et al., 2008). Moreover, menthol cigarette smokers have more difficulty quitting smoking and higher rates of relapse compared with their counterparts who smoke non-menthol tobacco (Ahijevych and Garrett, 2010; Besaratinia and Tommasi, 2015; Gardiner and Clark, 2010; Levy et al., 2011; Reitzel et al., 2013; Reitzel et al., 2011; Rojewski et al., 2014).

Our recent research, using the drug self-administration and reinstatement procedures that have showed good validities and translational value for our understanding of drug addictive behavior (Bossert et al., 2013; Henningfield et al., 2016 for exemplary reviews), demonstrated the impact of the interaction between menthol and nicotine on nicotine-addictive behavior. Specifically, menthol was found to enhance the reinforcing action of nicotine in a self-administration procedure (Biswas et al., 2016) and sustained and reinstated nicotine-seeking responses in an extinction-reinstatement paradigm (Harrison

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et al., 2017). However, the neurobiological mechanisms that underlie the observed behavioral effects of menthol and its interaction with nicotine remain unknown. The present study examined whether and the ways in which menthol interacts with nicotine to alter dopamine release in the brain reward system.

To make comparisons with the behavioral history of nicotine self-administration that was reported in our previous studies, the present study first allowed male Sprague-Dawley rats to intravenously self-administer nicotine (15 μg/kg/infusion) in daily 1-h sessions. Intracranial microdialysis coupled with high-performance liquid chromatography (HPLC) were then performed to measure dopamine levels in the right nucleus accumbens core (NAc). The NAc is an important terminal region of the brain mesocorticolimbic circuitry (Berridge and Robinson, 1998; Di Chiara and Bassareo, 2007; Ikemoto and Panksepp, 1999; Koob, 1992), which also plays a critical role in mediating the reinforcing actions of nicotine (Balfour et al., 1998; Clarke, 1990; Corrigall et al., 1992; Di Chiara, 2000; Picciotto and Corrigall, 2002; Watkins et al., 2000). We hypothesized that menthol would enhance the dopamine-releasing action of nicotine, but that menthol administration alone might not alter dopamine levels.

2. Materials and methods

2.1. Subjects

Male Sprague-Dawley rats were housed in a humidity- and temperature-controlled colony room on a reverse 12 h/12 h light/dark cycle. To facilitate nicotine self-administration learning and to be consistent with our previously reported behavioral data (Biswas et al., 2016), a food-restriction regimen (20 g chow/day) was employed with unlimited access to water throughout the experiments. The feeding regimen allowed the rats to have consistent but low weight gain (i.e., approximately 85% of their free-feeding weight). All of the experimental tests were conducted during the dark phase at the same time each day (9:00 AM–3:00 PM). The experimental protocol was approved by the University of Mississippi Medical Center Institutional Animal Care and Use Committee.

2.2. Surgical procedures

The rats were anesthetized with isoflurane (1–3% in 95% O_2 and 5% CO_2) and then underwent catheterization surgery. They were implanted with an indwelling intravenous catheter in the right jugular vein after lever-press training with food reward as previously reported (Biswas et al., 2016). These rats were also implanted with a unilateral guide cannula immediately after intravenous catheterization without the interruption of anesthesia. The rats were placed on a stereotaxic frame, and a stainless-steel guide cannula (CMA/Microdialysis) was implanted in the right NAc (1.7 mm anterior to bregma, 1.2 mm lateral to bregma, and 7.0 mm below the surface of the skull; (Paxinos and Watson, 2007). The concentric microdialysis probe (membrane length, 2 mm; outer diameter, 0.5 mm) was used to collect dialysate samples from the entire NAc region.

The rats were allowed to recover from surgery for 7–10 days. The catheters were flushed daily with 0.1 ml of sterile saline that contained heparin (30 U/ml) and gentamicin (20 mg/ml) to maintain catheter patency and prevent infection. Thereafter, the catheters were flushed with heparinized saline before and after the experimental sessions.

After performing microdialysis, probe placements were confirmed histologically. A representative microphotograph of a Cresyl violet stained brain section is shown in Fig. 1. Rats were excluded from the data analysis if more than half of the active portion of the dialysis membrane was outside the border of the NAc.

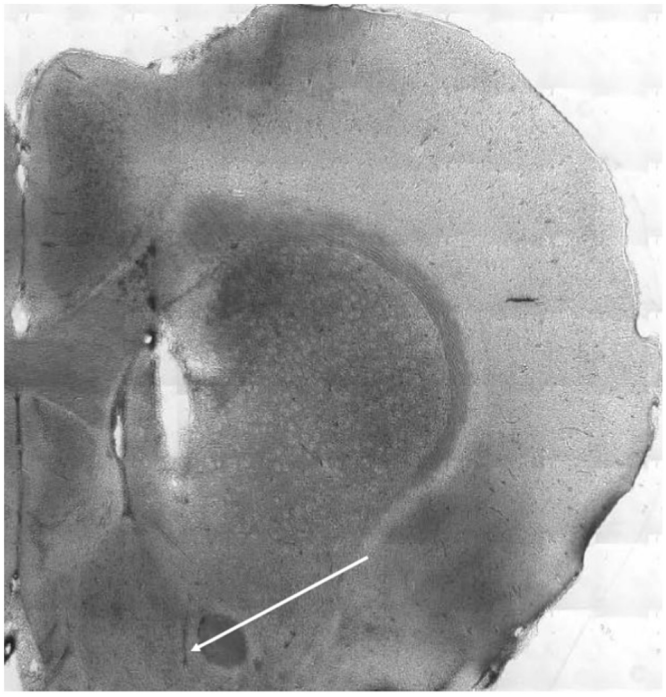

Fig. 1. A representative microphotograph of the brain section showing the placement of microdialysis probe in the nucleus accumbens core region.

2.3. Nicotine self-administration

The rats were allowed to intravenously self-administer nicotine (15 μg/kg/infusion, free base) in standard operant conditioning chambers (Med Associates, St. Albans, VT, USA) in 20 daily 1-h sessions. (-)-Nicotine hydrogen tartrate (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in physiological saline, and the pH was adjusted to 7.0 ± 0.4 with 1 N sodium hydroxide solution. The rats were placed in the operant conditioning chambers and connected to the intravenous drug infusion system. The sessions began with extension of the two levers into the chamber and illumination of a red house light. Once the rats reached the fixed-ratio (FR) requirement of responses on the active lever, an infusion of nicotine was delivered in a volume of 0.1 ml over approximately 1 s, depending on the rats' body weight. Each nicotine infusion was signaled by the presentation of an auditory/visual stimulus that consisted of 5-s tone and 20-s illumination of the light above the active lever, which also indicated a 20-s timeout period that followed each nicotine infusion. An FR1 schedule of reinforcement was used for sessions 1–5. An FR2 schedule was used for sessions 6–8. An FR5 schedule was used for sessions 9–20. Responses on the inactive lever were recorded but had no programmed consequences. The sessions were conducted 5 days/week with weekend off.

2.4. Microdialysis and dopamine assay

On the evening of the 20th day of nicotine self-administration, a microdialysis probe was inserted into the right NAc and perfused at 0.2 μl/min overnight. The next day (12–14 h after probe insertion), the rats were placed in the operant chambers, and the perfusion rate was increased to 2.0 μl/min. After 1-h equilibrium, dialysate sampling in 10-min fractions began and continued until the test was completed. Baseline sampling lasted 30 min, and then drug treatments were given at 60-min intervals. The dialysate samples were immediately frozen on dry ice and stored at −80 °C until the dopamine assay.

Dopamine concentrations in the dialysate samples were measured by reverse-phase HPLC coupled with electrochemical detection. The mobile phase was 0.54 nM monobasic sodium phosphate buffer that