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Sweet taste potentiates the reinforcing effects of e-cigarettes

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Abstract
Electronic cigarettes (e-cigarettes) are becoming increasingly popular. The popularity of fruit flavors among e-cigarette users suggests that sweet taste may contribute to e-cigarette appeal. We therefore tested whether sweet taste potentiates the reinforcing effects of nicotine. Using a conditioning paradigm adapted to study e-cigarettes, we tested whether exposure to flavored e-cigarettes containing nicotine plus sweet taste would be more reinforcing than unsweetened e-cigarettes. Sixteen light cigarette smokers smoked 4 distinctly colored e-cigarettes containing sweetened and unsweetened flavors with or without nicotine for 2 days each. Brain response was then assessed to the sight and smell of the 4 exposed e-cigarettes using fMRI. After exposure, sweet-paired flavors were wanted ($p = .024$) and tended to be liked ($p = .053$) more than nicotine-paired flavors. Moreover, sweet taste supra-additively increased liking for nicotine-paired flavors in individuals who did not show increased liking for nicotine alone ($r = -.67$, $p = .005$). Accordingly, cues predicting sweet compared to non-sweet flavors elicited a stronger response in the nucleus accumbens (NAcc, $p_{SVC} = .050$) and the magnitude of response to the sight ($p_{SVC} = .022$) and smell ($p_{SVC} = .017$) of the e-cigarettes correlated with changes in liking.

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By contrast, the sight and smell of cues predicting nicotine alone failed to elicit NAcc response. However, the sight and smell of e-cigarettes paired with sweet+nicotine ($p_{SVC} = .035$) produced supra-additive NAcc responses. Collectively, these findings demonstrate that sweet taste potentiates the reinforcing effects of nicotine in e-cigarettes resulting in heightened brain cue-reactivity.

1. Introduction

Organisms must procure energy to survive, and, as such, mechanisms have evolved to promote feeding. For example, sweet taste perception evolved to signal the availability of energy and promote its intake by producing a pleasant sensation and motivating ingestive behavior (de Araujo, 2011; Sclafani, 1987; Sheffield and Roby, 1950). The circuits that orchestrate such behaviors are therefore tuned to integrate sensory perceptions with post-ingestive reinforcing signals conveying nutritional information. In turn, organisms learn to like the available energy sources, leading to greater intake (de Araujo, 2016; de Araujo et al., 2013; Tellez et al., 2016). Whether sweet taste can interact with other reinforcers, such as nicotine, to promote consummatory behavior is unknown. However, this is an important gap in knowledge because tobacco products, including e-cigarettes, cigars, hookahs, and smokeless tobacco, are often consumed with sweet taste (Miao et al., 2016).

Alternative tobacco products such as e-cigarettes are becoming increasingly popular (Drummond and Upson, 2014). One appeal of e-cigarettes is that they often combine nicotine with sweet taste and flavors. In an online survey involving more than 5000 regular “vapers”, the top-ten flavors were characterized by sweet or fruity taste (http://ecigarettereviewed.com/best-e-juice-flavors). This raises the possibility that sweet flavors enhance the reinforcement potency of nicotine to promote e-cigarette use.

Supporting this possibility, for smokers, the aroma of nicotine-predictive tobacco is a potent cue that can promote smoking (Carpenter et al., 2014). Likewise, cross-sectional studies suggest that flavors increase the subjective value of e-cigarettes. For example, among an adolescent sample (Ambrose et al., 2015), most reported first using flavored products. Similarly, in a study of representative US 8th, 10th, and 12th graders, taste was found to be the second most important reason for e-cigarette use (Patrick et al., 2016) and was associated with a higher frequency of use (Patrick et al., 2016). Among adults, small-scale studies also point to the importance of sweet flavors, such as fruit, although to a lesser degree than in adolescents (Kim et al., 2016; Morean et al., 2017). With continued use, nicotine becomes a highly potent reinforcer primarily acting via nicotinic acetylcholine receptors that regulate dopamine release in the mesolimbic circuit (Changeux, 2010; Maskos et al., 2005; Tolu et al., 2013; Zhang et al., 2012). Nicotine also exerts long-lasting effects on reward sensitivity (Kenny and Markou, 2006). For example, nicotine amplifies firing of ventral tegmental area (VTA; Clark and Little, 2004; Tizabi et al., 2002) and NAcc shell neurons (Tizabi et al., 2007) in response to alcohol suggesting that nicotine can potentiate the reinforcement of other reinforcers. It is unknown whether this generalizes to sweet taste or, vice versa, if sweet taste amplifies the reinforcing effect of nicotine by increasing flavor liking or wanting. However, nicotine use is associated with differential responses in feeding circuits to food-related stimuli in humans (Geha et al., 2013; Kroemer et al., 2013) and activation of nicotinic acetylcholine receptors in feeding circuits alters appetite in rodents (Mineur et al., 2011). Taken together, data suggest that taste contributes to the reinforcing effects of nicotine-containing e-cigarettes and raise the possibility that the combination of two reinforcers may enhance the appeal of the product.

If such interactions occur, the NAcc is a likely substrate. Both food and smoking cues reliably induce BOLD responses in the NAcc (Tang et al., 2012). NAcc mu-opioid hedonic “hotspots” are implicated in subjective pleasure (Berridge and Kringelbach, 2015; Castro and Berridge, 2014; Kelley et al., 2002) and striatal dopamine plays a key role in reward-related learning (Kroemer and Small, 2016; O’Doherty et al., 2004; Pessiglione et al., 2006; Schonberg et al., 2007; Steinberg et al., 2013; Valentin and O’Doherty, 2009; Veldhuizen et al., 2011). In line with animal studies, smoking induces dopamine release in the NAcc (Brody et al., 2004) and short-term abstinence from smoking increases BOLD responses to cigarette puffs as reward in the caudate head and NAcc (Sweitzer et al., 2014). Moreover, Pavlovian cues have been found to increase instrumental responding via dopamine D1 and D2 receptors in the NAcc (Lex and Hauber, 2008), thus entailing the potential to modulate behavior such as e-cigarette use. Collectively, these studies suggest that the addition of sweet taste could potentiate the addictive liability of tobacco products because both reinforcers act via shared neural pathways.

To test whether the reinforcing effects of sweet taste and nicotine interact to enhance reward from e-cigarettes, we adapted a flavor-nutrient conditioning paradigm for use with e-cigarettes (de Araujo et al., 2013). Participants were exposed to four novel e-cigarette flavors that varied in sweetness (sweetened or unsweetened) and nicotine content (with or without; 2×2 design). The reinforcing effects of the nicotine and/or sweet predicting conditioned flavors were then measured by assessing liking and wanting ratings and brain responses to the sight and the smell of the predictive e-cigarette flavors (i.e. in the absence of sweet taste and nicotine). Liking reflects hedonic aspects of conditioning, whereas wanting has been shown to be a good predictor of actual drug consumption (Ostafin et al., 2010). In addition, brain response to food and nicotine-related cues is a reliable predictor of behavioral outcomes reflecting reinforcement such as weight gain (Sun et al., 2015),