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Brief communication

Title:

Rapid Brain Nicotine Uptake from Electronic Cigarettes

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Short title: Brain nicotine uptake from E-cig use

Abstract

This study sought to determine brain nicotine kinetics from the use of increasingly popular electronic cigarettes (E-cigs). **Methods:** Brain uptake of nicotine following inhalation from E-cigs was directly assessed in 17 E-cig users (8 females), using ^{11}C-nicotine and positron emission tomography. The brain nicotine kinetics parameters from E-cigs were compared with those from smoking combustible cigarettes (C-cigs). **Results:** After inhalation of a single puff of E-cig vapor, brain nicotine concentration rose quickly (mean $T_{1/2}$ 27 sec) with a peak amplitude 25% higher in females than males, resembling previous observations with C-cigs. Nonetheless, brain nicotine accumulation from E-cigs was smaller than that from C-cigs in both males and females (24% and 32%, respectively). **Conclusion:** E-cigs can deliver nicotine to the brain with similar rapidity as C-cigs. Therefore, to the extent that rapid brain uptake promotes smoking reward, e-cigarettes might maintain a degree of nicotine dependence and also serve as non-combustible substitutes for cigarettes.

Keywords: Nicotine, electronic cigarettes, e-cigarettes, ENDS, smoking, vaping

Introduction

Recently, there has been enormous growth in the popularity of electronic cigarettes (E-cigs; *1, 2*). While E-cigs are likely less harmful than combustible cigarettes (C-cigs), a concern is that use of these products can lead to the development and maintenance of nicotine dependence. As with other abused drugs, the rate and magnitude of brain nicotine accumulation may contribute importantly to its acute reinforcing effects (*3-9*). The proposed continuum of nicotine-containing products' abuse liability (*10*) is quite close to the continuum of the rapidity of nicotine delivery to the brain (highest for cigarettes and lowest for nicotine patches). In several recent studies (*11-13*) performed in experienced E-cig users, increases in venous blood nicotine concentration after E-cig use were comparable to those after cigarette smoking. Venous concentrations, however, do not accurately reflect brain levels, and the capability of E-cigs to produce fast nicotine delivery to the brain, as previously observed with C-cigs (*14-15*), has not been studied. Here, we report the results of a first direct assessment of brain uptake of nicotine from E-cig use. Sex differences were also examined in view of previously observed sex differences in brain nicotine accumulation with C-cigs (*16*).

Materials and Methods

PET scanning following inhalation of E-cig vapor was conducted in 17 E-cig users, three of whom were also scanned after they inhaled C-cig smoke at a separate session. For comparison, PET data from 19 C-cig smokers who completed a previously reported study (*16*) were also included for the present analysis. Participants in each group were recruited from the Winston-Salem, NC area. Inclusion criteria consisted of 18-65 years of age, being generally healthy, using E-cigs ≥ 4 times per month (for the E-cig group) or smoking ≥ 8 cigarettes per day (for the C-cig

group). Exclusion criteria included respiratory or cardiovascular diseases, psychiatric disorders, alcohol abuse, illicit drug use, or contraindications for PET scan (e.g., pregnancy). There were 8 current smokers, 8 ex-smokers, and 1 never-smoker in the E-cig group. The two groups were comparable in sex (male/female: 9/8 vs. 9/10) and racial (Caucasian/African-American/others: 70.6%/17.6%/5.9% vs. 73.7%/26.3%/0) composition (χ^2 tests, n.s.), age (mean ± SD; 43 ± 13 vs. 44 ± 10 years), body weight (87 ± 16 vs. 82 ± 19 kg), and years of smoking (21 ± 14 vs. 24 ± 12), respectively (t-tests, n.s.). The Institutional Review Board of the Duke University Health System and the Institutional Review Board of the Wake Forest University Health Sciences approved this study and all subjects signed a written informed consent.

Each participant went through a PET scanning session during which the head was scanned after he/she inhaled a single puff of vapor or smoke containing ^{11}C-nicotine. A standardized puff of vapor was produced from 15 μL V2 Red e-liquid (1.2% nicotine, 20/80 VG/PG) mixed with ^{11}C-nicotine via a V2 EX Blanks refillable cartomizer (V2 E-cig products currently available at migvapor.com) coupled with a programmable air syringe pump. The smoke was generated from a shortened Basic Gold 100's hard pack cigarette (Philip Morris, USA) through a customized smoke delivery device after ^{11}C-nicotine was applied (*16,17*). The subject's head was scanned for just over 12 min in a sequence of 245 frames of 1~4 sec each. Afterwards, a full-body scan was conducted to measure total absorbed dose of ^{11}C-nicotine (TAD), which was used to normalize the ^{11}C-nicotine uptake values between-subjects and between conditions. ^{11}C-nicotine was synthesized following an established protocol (*18*). The PET scans were conducted using a GE Discovery MI DRPET/CT scanner (Waukesha, WI). PET image processing was conducted using PMOD (Zurich, Switzerland). Whole-brain ^{11}C-nicotine radioactivity over time was calculated as a percentage of TAD per kg of brain tissue. After the individual brain time activity

curves were subjected to three-exponential curve fitting (*11*), values of kinetics parameters (i.e., C_{max}, AUC, and $T_{1/2}$) were calculated.

Analysis of variance (ANOVA) with two between-subject factors (E-cig vs. C-cig; sex) was conducted on each of the three parameters of brain nicotine accumulation following the inhalation of smoke or vapor containing ^{11}C-nicotine. Additional ANCOVAs with years of smoking or body weight, each entered as a covariate, were also performed given possible effects of either variable on nicotine kinetics. Threshold for statistical significance was set at $p < 0.05$ (2-tailed). Group mean values (± SEM) are reported unless otherwise specified.

Results

The average brain ^{11}C-nicotine activity curves measured with PET in 17 E-cig users and 19 smokers after inhalation of a single-puff of E-cig vapor (n=17) or cigarette smoke (n=19) are shown in Fig. 1A, B. Both product group and sex were significant factors affecting maximum brain nicotine concentration ($C_{max;}$ Fig. 1C) and area under curve (AUC; Fig. 1D). Mean C_{max} and AUC values were lower in the E-cig vs. C-cig condition by 30.4% (for men/women: 24.2%/32.3%) and by 28.9% (for men/women: 24.7%/30.2%), respectively.

C_{max} and AUC values following E-cig vapor inhalation were 24.6% and 25.3% greater in women than in men, respectively, which is similar to our observation with C-cigs (32.7% and 31.6%, respectively). Mean time to reach 50% of C_{max} ($T_{1/2}$) showed no significant differences between the two products. A trend for shorter $T_{1/2}$ in women than in men ($p = 0.065$; 22.5 ± 5.0 vs 30.8 ± 5.4 s for E-cig; 19.1 ± 2.2 vs 27.8 ± 4.8 s for C-cig) was observed. No product × sex interaction was found with any of the three kinetics parameters.

The differences in brain nicotine kinetics between these two products and between sexes remained statistically robust in additional ANCOVA analyses with either body weight or years of smoking entered as a covariate.

Comparison of whole body distribution of the radioactivity after inhalation from E-cigs or C-cigs revealed higher oropharyngeal/tracheobronchial deposition of nicotine after E-cig use. To illustrate this observation, we performed two whole body PET scans in three participants, each inhaling E-cig vapor and C-cig smoke in separate sessions. A representative result is shown in Fig. 2.

Discussion

Three important and new findings from this study are: (i) E-cigs can deliver nicotine to the brain with similar rapidity as C-cigs; (ii) the magnitude of brain nicotine accumulation from E-cigs in both males and females was ca. 30% smaller that from C-cigs; and (iii) the magnitude of brain nicotine accumulation after E-cig use in females is ca. 24% higher than that in males, resembling the sex difference previously reported for C-cigs.

After inhalation of a single puff of E-cig vapor, brain nicotine concentration rose quickly, similar to that after a puff from C-cigs (mean $T_{1/2}$ values 27 ± 4 sec and 23 ± 3 sec). This temporal profile suggests that the primary route of nicotine delivery to the blood after E-cig use is alveolar absorption, leading to the rapid rise of nicotine concentration in arterial blood. Nonetheless, the C_{max} and AUC values for E-cig were 2/3 of those for C-cig. Since brain nicotine uptake is a regional cerebral blood-flow (rCBF) dependent process (19-21), these differences could be explained by slower brain blood perfusion and/or lower arterial blood nicotine concentration after using E-cigs. While both of these explanations remain to be verified in the

future studies, our preliminary whole-body imaging results suggest that the lower brain nicotine accumulation following E-cig use relative to C-cig smoking can be at least partially attributed to the lower arterial blood nicotine concentration from E-cigs due to greater nicotine retention from the vapor versus cigarette smoke in the upper respiratory tract, resulting in less nicotine reaching the alveoli where rapid absorption occurs. A possible explanation is that the typical more alkaline pH of E-cig liquids than C-cig smoke (pH 7-9 for E-cig and 5-6 for C-cig (22, 23)) enhances evaporation of nicotine base from droplets and its retention in the respiratory tract. Such deposition of nicotine is likely to be reduced by using E-cig liquid with low pH.

The observed more intensive brain nicotine accumulation from E-cig in females than males might reflect sex differences in respiratory tract anatomy (*16*) and/or in hemodynamics. Since brain nicotine accumulation is a blood flow-dependent process (*19-21*), the higher brain nicotine accumulation in females might be explained by a ca. 35% higher ratio of cerebral blood flow to cardiac output in females than in males (*24*). It should be noted that the slower brain nicotine delivery by E-cigs can be compensated by higher nicotine content of e-liquids and/or by more intensive vaping to achieve a desired effect.

Conclusion

These results suggest that E-cigs can deliver nicotine to the brain with similar rapidity as C-cigs and that there is a sex difference in this delivery. Therefore, to the extent that rapid brain uptake promotes smoking reward, E-cigs might maintain a degree of nicotine dependence and also serve as non-combustible substitutes for cigarettes.

Disclosure

This research was supported by the NIH (R01 DA044756, R03 DA029676, P30 CA012197-35, UL1 TR001420, UL1 TR001873) and American Cancer Society (124443-MRSG-13-121-01-CDD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or American Cancer Society. Dr. Rose reports grants from JUUL Labs Inc., grants, personal fees and patent purchase agreement on a nicotine delivery system with Philip Morris International, grants from Altria, grants and personal fees from Intratab Labs Inc., grants from National Institute on Drug Abuse, personal fees from Embera Neurotherapeutics, outside the submitted work. In addition, Dr. Rose has a patent on a nicotine delivery system licensed. Other authors have nothing to disclose.

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KEY POINTS

Question: This study sought to determine brain nicotine kinetics from the use of increasingly popular electronic cigarettes.

Pertinent Findings: Brain uptake of nicotine following inhalation from electronic cigarettes was directly assessed in 17 electronic cigarette users (8 females), using ^{11}C-nicotine and positron emission tomography. The parameters of brain nicotine kinetics from using electronic cigarettes were compared with those from smoking combustible cigarettes. Electronic cigarettes delivered nicotine to the brain with similar rapidity as combustible cigarettes. Nonetheless, brain nicotine accumulation from electronic cigarettes was smaller than that from combustible cigarettes in both males and females (24% and 32%, respectively). The observed slightly smaller brain nicotine delivery by electronic cigarettes can be compensated by higher nicotine content of e-liquids and/or by more intensive vaping to achieve a desired effect.

Implications for Patient Care: To the extent that rapid brain uptake promotes smoking reward, electronic cigarettes might maintain a degree of nicotine dependence and also serve as non-combustible substitutes for cigarettes.

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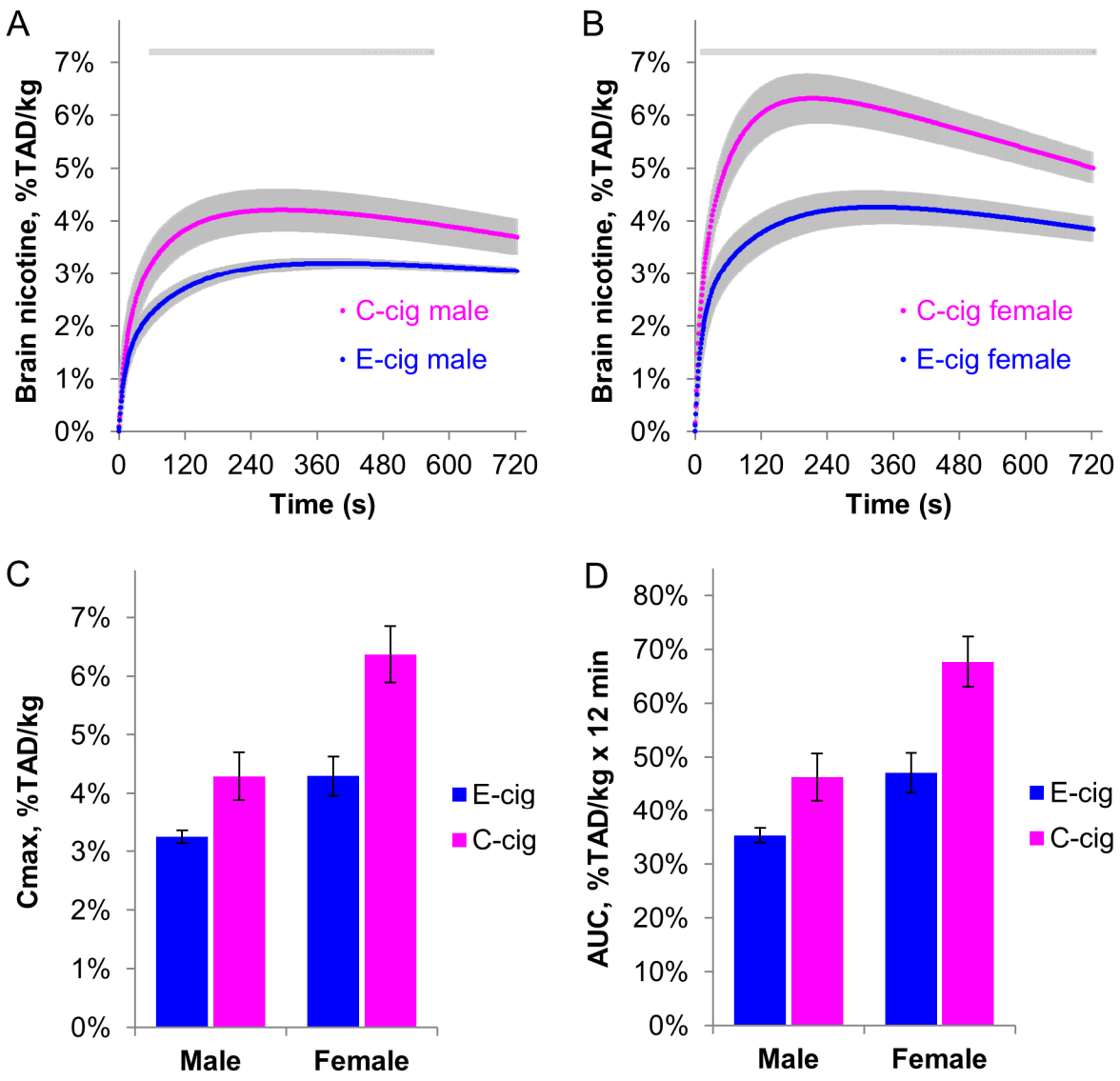

Figure 1. Average brain nicotine accumulation curves and kinetics parameters (Mean ± SEM) after participants' inhalation of a single puff of e-cigarette (E-cig) vapor (n = 17, 8 females) or conventional cigarette (C-cig) smoke (n = 19; 10 females) containing ^{11}C-nicotine. Gray straight lines in A and B represent the time interval when the difference between the products was statistically significant (*t*-test, $p < 0.05$). Mean maximum brain ^{11}C-nicotine concentration (C_{max}) and area under curve (AUC) differed between the two products ($p = .0002$; $p = .0003$, respectively) and sexes ($p = .0002$; $p = .0001$) but without interactions of these two factors. Brain nicotine accumulation per kg of tissue mass was expressed as a percentage of the total absorbed dose (TAD) of ^{11}C-nicotine.

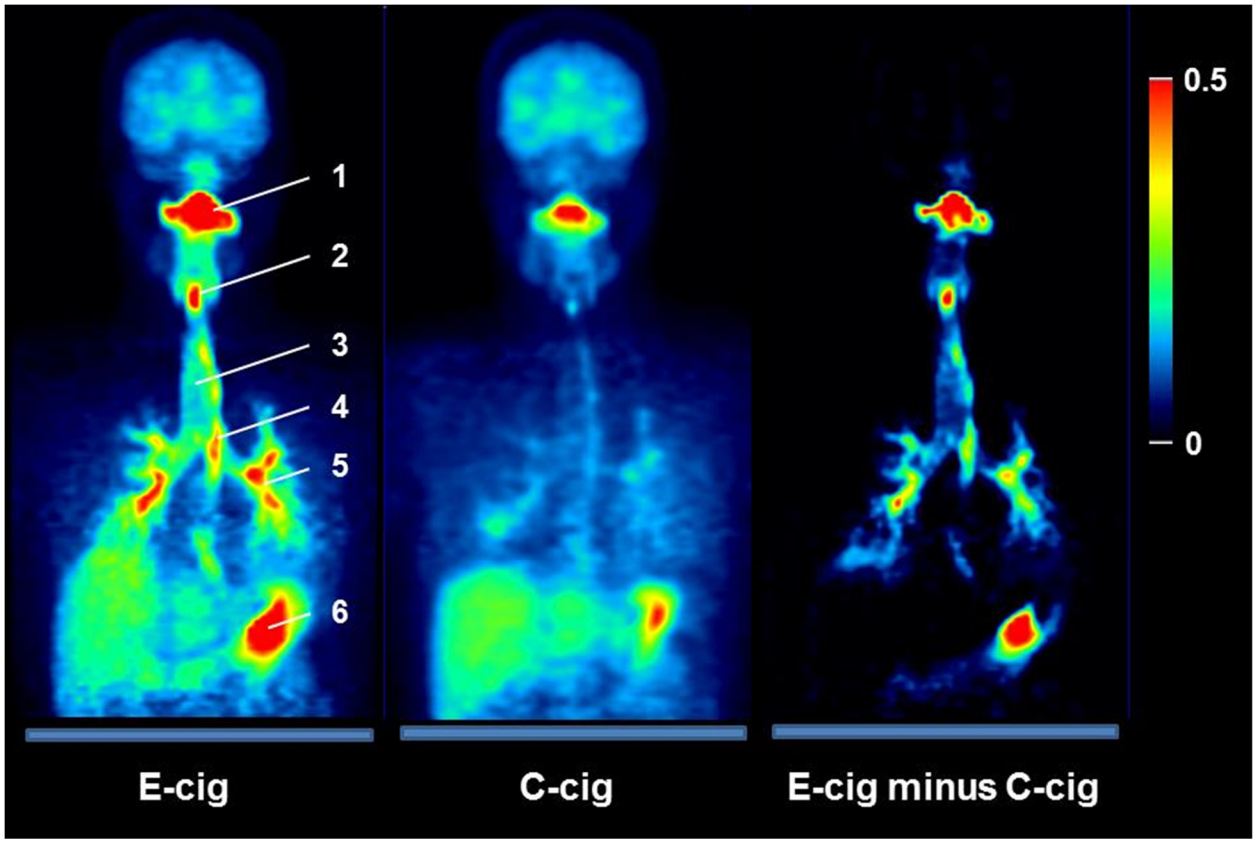

Figure 2. Oropharyngeal/tracheobronchial deposition of nicotine after using E-cig and C-cig. The images are presented as a sum of the coronal slices of 3D radioactivity distribution assessed at 18 min after inhalation of a single puff from the respective ^{11}C-nicotine containing product and expressed as % total absorbed dose (TAD)/kg tissue. The max value of the pseudo-color scale is 0.5 % TAD/cm^2. 1 – mouth cavity; 2 – vocal cords; 3 – trachea; 4 – esophagus; 5 – bronchi; and 6 – stomach. Right image show the between-conditions differences. The subtraction E-cig image from C-cig image did not show specific places where C-cig produced visibly greater nicotine concentration than E-cig (image is not shown); rather there was a slight increase in nicotine concentration throughout the body outside of the respiratory tract for the C-cig condition.