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Effects of nicotine and minor tobacco alkaloids on intracranial-self-stimulation in rats

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Abstract

Background—While nicotine is the primary addictive compound in tobacco, other tobacco constituents including minor alkaloids (e.g., nornicotine, anabasine) may also contribute to tobacco addiction by mimicking or enhancing the effects of nicotine. Further evaluating the behavioral effects of minor alkaloids is essential for understanding their impact on tobacco addiction and informing development of tobacco product standards by the FDA.

Methods—This study compared the addiction-related effects of nicotine and the minor alkaloids nornicotine, anabasine, myosmine, anatabine, and cotinine on intracranial self-stimulation (ICSS) thresholds in rats.

Results—Acute injection of nicotine produced reinforcement-enhancing (ICSS threshold-decreasing) effects at low to moderate doses, and reinforcement-attenuating/aversive (ICSS threshold-increasing) effects at high doses. Nornicotine and anabasine produced similar biphasic effects on ICSS thresholds, although with lower potency compared to nicotine. Myosmine only elevated ICSS thresholds at relatively high doses, while anatabine and cotinine did not influence

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Contributors. Mark LeSage and Andrew Harris supervised the conduct of the study and were responsible for the conception and design of the study. Laura Tally, Peter Muelken, Andrew Banal, and Clare Schmidt assisted with developing specific protocols, daily conduct of the experiment, and compiling data. Qing Cao contributed to the statistical analysis. Andrew Harris wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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ICSS thresholds at any dose. None of the alkaloids significantly influenced ICSS response latencies, indicating a lack of nonspecific motoric effects.

Conclusions—These findings indicate that some minor tobacco alkaloids can either fully (nornicotine, anabasine) or partially (myosmine) mimic nicotine's addiction-related effects on ICSS, albeit at reduced potency. These findings emphasize the need for further study of the abuse potential of minor alkaloids, including evaluation of their effects when combined with nicotine and other tobacco constituents to better simulate tobacco exposure in humans. Such work is essential for informing FDA regulation of tobacco products and could also lead to the development of novel pharmacotherapies for tobacco addiction.

Keywords

Nicotine; minor alkaloids; non-nicotine tobacco constituents; intracranial self-stimulation; rat

1. INTRODUCTION

The primary role of nicotine in maintaining tobacco use is well established (Benowitz, 2008; U.S. Department of Health and Human Services, 1999), but non-nicotine tobacco constituents may also contribute to tobacco addiction. For example, minor tobacco alkaloids (e.g., nornicotine, anabasine) can mimic nicotine's behavioral and neuropharmacological effects, albeit typically at reduced potency compared to nicotine (for review, see Brennan et al., 2014; Hoffman and Evans, 2013). Further evaluation of minor alkaloids is essential for understanding their impact on tobacco addiction and could lead to the development of novel pharmacotherapies for smoking cessation. Given that the Food and Drug Administration (FDA) now has the authority to regulate the content of nicotine and other constituents in tobacco products (Deyton et al., 2010; Hatsukami et al., 2012, 2010), such work could also inform the development of tobacco product standards to reduce the addictiveness of those products (Benowitz and Henningfield, 1994, 2013; Henningfield et al., 2004).

Intracranial self-stimulation (ICSS) has been useful for studying the addiction-related effects of drugs on brain reinforcement systems. Low to moderate doses of nicotine and other drugs reduce the minimal (threshold) stimulation intensity that maintains ICSS, suggesting increased sensitivity to the reinforcing effects of the brain stimulation (Caggiula et al., 2009; Harrison et al., 2002; Huston-Lyons and Kornetsky, 1992). This effect may reflect the more general ability of drugs to enhance the reinforcing effects of environmental stimuli (*e.g.*, sensory stimuli, food; see Caggiula et al., 2009; Chaudhri et al., 2006; Paterson et al., 2008; Wise, 2002), an important behavioral mechanism mediating drug addiction (Caggiula et al., 2009; Chaudhri et al., 2006; Paterson, 2009). The ability of drugs to reduce ICSS thresholds is potentially more predictive of their abuse liability than other measures. For example, some drugs of abuse that are not self-administered (e.g., hallucinogens) nonetheless reduce ICSS thresholds (Wise, 1996, 2002; Wise et al., 1992). High doses of nicotine and other drugs inhibit the function of brain reinforcement systems and elevate ICSS thresholds, a putative measure of aversion (Fowler et al., 2011; Kenny et al., 2003; Spiller et al., 2009). A drug's aversive effects are an important component of its abuse liability because they limit the amount of drug consumed (for review, see Fowler and Kenny, 2013; Verendeev and Riley, 2013).

Despite the utility of ICSS in the study of drug addiction, effects of minor alkaloids have not been examined in this model. To this end, the current study evaluated the acute effects of nicotine and the minor alkaloids nornicotine, anabasine, myosmine, anatabine, and cotinine on ICSS thresholds. Although nornicotine has been studied most extensively (e.g., Bardo et al., 1999; Dwoskin et al., 1999; Green et al., 2000), all of these minor alkaloids can produce behavioral effects under some conditions (Caine et al., 2014; Clemens et al., 2009; Goldberg et al., 1989; Hall et al., 2014; Pratt et al., 1983; Stolerman et al., 1995; Stolerman et al., 1984).

2. METHODS

2.1. Animals

Experimentally-naive male Holtzman Sprague Dawley rats (Harlan, Indianapolis, IN) weighing 250–300 g upon arrival in the colony were housed individually under a reversed 12-hr light/dark cycle and allowed unlimited access to water. All testing occurred during the dark (active) phase. Beginning one week after arrival, rats were food-restricted to ≈18 g/day rat chow to facilitate operant performance and avoid detrimental effects of long-term ad libitum feeding on health. Animals were postnatal day (PND) 144 ± 13.5 (mean ± SEM) at the onset of alkaloid dosing (described below) and, among those rats completing the entire protocol, PND 301.8 ± 23.1 at the completion of the study. Protocols were approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation in accordance with the 2011 NIH Guide for the Care and Use of Laboratory Animals and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council 2003).

2.2. Drugs

(−)-Nicotine bitartrate, (+/−) nornicotine, (+/−) anabasine, (+/−) myosmine, and (−)-cotinine were obtained from Sigma (St Louis, MO). (+/−) Anatabine was obtained from Toronto Research Chemicals, Inc. (Ontario, Canada). All drugs were prepared in sterile saline, adjusted to a pH of 7.4 using dilute NaOH, and administered s.c. in a volume of 1 ml/kg. All drug doses are expressed as the base.

2.3. Intracranial self-stimulation

Surgery, apparatus, and training procedure used here are described in detail elsewhere (Harris et al., 2013, 2010, 2011; Manbeck et al., 2013). Briefly, animals were anesthetized with i.m. ketamine (75 mg/kg)/xylazine (7.5 mg/kg) and implanted with an electrode in the medial forebrain bundle at the level of the lateral hypothalamus. Rats were later trained to respond for electrical brain stimulation using a modified version of the Kornetsky and Esposito (1979) discrete-trial current-threshold procedure (Markou and Koob, 1992). Each session was approximately 45 minutes and provided two dependent variables: ICSS thresholds (a measure of brain reinforcement function) and response latencies (a measure of non-specific (*e.g.*, motoric) effects).

2.4. Protocol

Animals (N = 15) were tested in daily ICSS sessions conducted Mon-Fri until thresholds were stable (less than 10% coefficient of variation over a 5-day period and no apparent trend). To habituate animals to the injection procedure, saline was administered 10 minutes prior to ICSS testing twice per week (Tuesdays and Fridays) for at least 1 session and until thresholds were stable. Effects of 10-minute pretreatment with nicotine were subsequently determined at nicotine doses of 0, 0.125, 0.25, 0.50, or 1.0 mg/kg. These nicotine doses reduce or increase ICSS thresholds when administered acutely (e.g., Harris et al., 2015; Harrison et al., 2002; Huston-Lyons and Kornetsky, 1992). Injections typically occurred on Tuesdays and Fridays, provided that thresholds were within baseline range on intervening days, and doses were administered in a counterbalanced order.

Following completion of nicotine dose-response testing, animals were tested for ICSS under drug-free conditions for at least 2 weeks and until ICSS thresholds were stable. Dose-response determinations for a total of five minor alkaloids were conducted. For each rat, three minor alkaloids were randomly chosen to be tested, with each dose-response determination separated by at least a two-week washout period and attainment of stable ICSS thresholds. Test sessions were conducted as described for nicotine, except that rats received 10-minute pretreatment with nornicotine (0, 0.5, 1.0, 3.0, or 6.0 mg/kg), anabasine (0, 0.5, 1.0, 3.0, or 4.0 mg/kg), myosmine (0, 1.0, 6.0, 10.0, or 15.0 mg/kg), anatabine (0, 0.25, 0.5, 1.0, or 3.0 mg/kg), or cotinine (0, 1.0, 6.0, 10.0, or 100.0 mg/kg). These doses were not chosen based on their clinical relevance, as they are considerably higher than those delivered during actual tobacco use (e.g., quantities of nornicotine in the smoke of one cigarette ranged from 27–88 pg, see U.S. Public Health Service, 1988). Rather, they were chosen based on their behavioral effects reported in other animal models of tobacco addiction and to establish the effective dose range in the present model (Caine et al., 2014; Dwoskin et al., 1999; Goldberg et al., 1989; Hall et al., 2014; Stolerman et al., 1995, 1984). Doses and pretreatment time were also based on a pilot study examining acute effects of these minor alkaloids on ICSS (data not shown).

2.5. Statistics

Intracranial self-stimulation thresholds (in μA) and response latencies (in seconds) were expressed as percentage of baseline (i.e., mean during last 5 sessions prior to each dose-response determination). Data for each alkaloid condition were subsequently analyzed using a one-factor, repeated measures ANOVA, followed by a Dunnett post hoc test comparing each alkaloid dose to saline. Degrees of freedom for ANOVAs were adjusted using the method of Geisser and Greenhouse to correct for any violations of sphericity. In the two cases in which rats failed to respond for any ICSS current intensity (both observed following administration of 4.0 mg/kg anabasine), we arbitrarily assigned an ICSS threshold value of 206.0% and a latency value of 132.0%. These threshold and latency values were used because they were slightly larger than those obtained in the animal achieving the highest ICSS threshold throughout the entire experiment. This approach has previously been used to account for missing ICSS data under analogous conditions (see Markou and Koob, 1991).

3. RESULTS

3.1 Attrition and baseline measures

Due to attrition caused by removal of an ICSS headcap or loss of stability of ICSS thresholds, data for some animals were available for only one (n = 3) or two (n = 3) of their three assigned minor alkaloids. Data for the remaining 9 animals were available for all three of their assigned minor alkaloids.

Mean baseline thresholds and response latencies ranged from 96.7 –109.0 μA and 2.3 – 2.5 seconds, respectively, across the different alkaloid dose-response determinations.

3.2. ICSS thresholds

There was a significant effect of dose for the nicotine condition ($F(2.6, 36.3)=23.3$, $p<0.0001$), with ICSS thresholds significantly reduced compared to saline at 0.125 mg/kg ($q(14) = 5.7$, $p < 0.01$) and 0.25 mg/kg ($q(14) = 2.9$, $p < 0.05$) and elevated compared to saline at 1.0 mg/kg ($q(14) = 6.0$, $p < 0.01$) (Fig 1A).

For the minor alkaloids, there was a significant effect of dose for the nornicotine condition ($F(2.0,14.0)=11.4$, $p = 0.0012$), anabasine condition ($F(1.6,11.0)=16.5$, $p = 0.0008$), and myosmine condition ($F(2.5,17.5) = 4.4$, $p = 0.0224$) (see Fig 1B–1D). For nornicotine, ICSS thresholds were significantly reduced compared to saline at 0.5 mg/kg ($q(7) = 3.9$, $p < 0.05$) and 1.0 mg/kg ($q(7) = 3.7$, $p < 0.05$) and elevated compared to saline at 6.0 mg/kg ($q(7) = 3.9$, $p < 0.05$) (Fig 1B). For anabasine, ICSS thresholds were significantly reduced compared to saline at 1.0 mg/kg ($q(7) = 3.8$, $p < 0.05$) and elevated at 4.0 mg/kg ($q(7) = 4.2$, $p < 0.05$) (Fig 1C). Myosmine did not reduce ICSS thresholds compared to saline at any dose, but elevated thresholds at 15.0 mg/kg ($q(7) = 4.7$, $p < 0.01$) (Fig 1D). Although anatabine appeared to produce a modest biphasic effect on thresholds (Fig 1E), the effect of anatabine dose was not significant ($F(2.5,14.9) = 2.6$, $p = 0.10$) and no dose of anatabine differed significantly from saline ($q(6) = 1.0 – 1.8$, $p = 0.30–0.73$). There was also no significant effect of dose for the cotinine condition ($F(2.8,13.8) = 0.82$, $p = 0.50$), and no dose of cotinine differed from saline ($q(5) = 0.16 – 0.93$, $p = 0.77–0.99$; Fig 1F).

3.3 ICSS latencies

Among all alkaloids studied (Fig 2A–2F), ANOVA indicated a significant effect of dose on response latencies for only nornicotine ($F(2.3,16.1)= 4.1$, $p = 0.032$; Fig 2B). However, follow-up pairwise comparisons showed that latencies did not differ significantly from saline at any nornicotine dose (all p-values ≥ 0.063, see Fig 2B).

4. DISCUSSION

This study provides new information on the addiction-related effects of the minor tobacco alkaloids nornicotine, anabasine, myosmine, anatabine, and cotinine on ICSS in rats. As expected, nicotine produced reinforcement-enhancing (ICSS threshold-decreasing) effects at low to moderate doses, and reinforcement-attenuating/aversive (ICSS threshold-increasing) effects at high doses. Nornicotine and anabasine produced similar biphasic effects on ICSS thresholds, although with lower potency compared to nicotine. Myosmine only elevated

thresholds at high doses, while anatabine and cotinine did not affect ICSS thresholds. None of the alkaloids significantly affected ICSS response latencies, indicating a lack of non-specific motoric effects.

Our findings extend previous reports that nornicotine and anabasine can mimic nicotine's effects in other behavioral models (e.g., nicotine discrimination; Dwoskin et al., 1999; Goldberg et al., 1989; Green et al., 2000; Pratt et al., 1983). The ≈ 5–10 fold lower potency of nornicotine and anabasine compared to nicotine was similar to that reported in some of these studies (e.g., Dwoskin et al., 1999). Together, these findings support nornicotine and anabasine as potential targets for smoking cessation medication development and establishment of tobacco product standards by the FDA. To the extent that the present findings are indicative of the abuse potential of nornicotine and anabasine, they support the inclusion of these compounds on the FDA's list of harmful and potentially harmful constituents in tobacco products and tobacco smoke (Food and Drug Administration, 2012).

Limited data are available on the behavioral effects of myosmine, anatabine, and cotinine. A cocktail containing these three minor alkaloids, in addition to nornicotine and anabasine, did not itself maintain i.v. self-administration or influence locomotor activity, but potentiated nicotine's reinforcing and locomotor stimulant effects (Clemens et al., 2009). Myosmine, anatabine, or cotinine alone also potentiated nicotine's locomotor stimulant effects in Clemens et al. (2009). Other studies have reported that myosmine, anatabine, and cotinine can produce nicotine-like behavioral effects (Caine et al., 2014; Goldberg et al., 1989; Hall et al., 2014; Wiley et al., 2015). However, some of these effects were partial, not related to dose, and/or only observed at very high doses that may have produced toxicity or contained nicotine as an impurity. Taken together with the current data, these findings suggest that the abuse liability of myosmine, anatabine, and cotinine may be limited. However, further behavioral and neurobiological characterization of these minor alkaloids is clearly warranted. For example, the non-significant trend for anatabine to produce a biphasic effect on ICSS thresholds (see Fig 5E) could be further explored using larger sample sizes to confirm this pattern of effects.

We recently reported that nicotine alone and nicotine dose-equivalent concentrations of smokeless tobacco extracts produced similar acute effects on ICSS thresholds (Harris et al., 2015). Those extracts contained levels of nornicotine and anabasine more representative of exposure levels in smokeless tobacco users and that were at least 33- and 125-fold lower, respectively, than those shown to have behavioral effects in the current studies (see Table 2 in Harris et al., 2015). The lack of differences between nicotine alone and extracts in this study may therefore not be particularly surprising. Nonetheless, nicotine and non-nicotine constituents can produce additive or synergistic effects when administered in combination as occurs during actual tobacco use (Arnold et al., 2014; Belluzzi et al., 2005; Clemens et al., 2009). As such, regardless of their effects when studied in isolation, all of the current minor alkaloids could influence ICSS through interactions with nicotine, other minor alkaloids, and/or other behaviorally relevant tobacco constituents (e.g., acetaldehyde). Examining the effects of variations in tobacco constituent cocktails is needed to better understand the potential role of minor alkaloids in the abuse liability of tobacco products.

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Highlights

1. We tested effects of tobacco alkaloids on intracranial self-stimulation (ICSS).
2. Moderate nicotine doses reduced while high nicotine doses increased ICSS thresholds.
3. Nornicotine and anabasine produced similar effects, although with lower potency.
4. High-dose myosmine elevated thresholds, while anatabine and cotinine had no effect.
5. Some minor alkaloids can either fully or partially mimic nicotine's effects on ICSS.

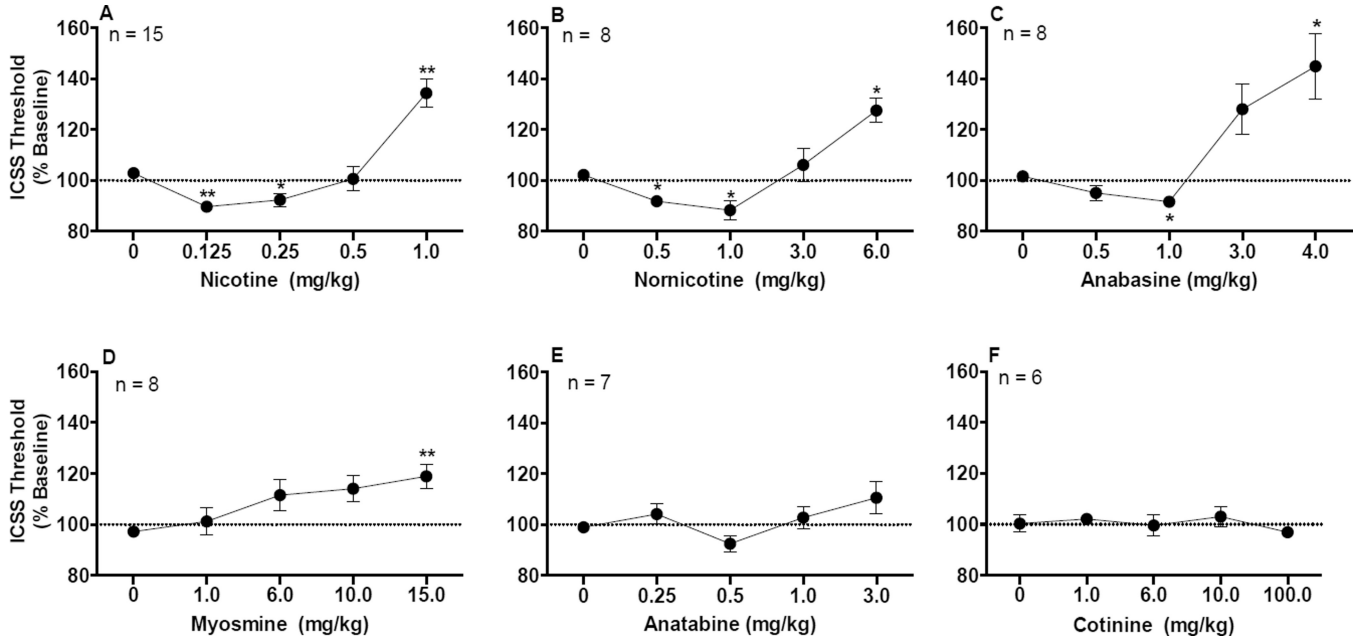

Figure 1.

ICSS thresholds (expressed as percent of baseline, mean ± SEM) following injection of nicotine (A), nornicotine (B), anabasine (C), myosmine (D), anatabine (E), or cotinine (F). Number of animals tested with each alkaloid is also shown. *,** Significantly different from saline (0 mg/kg) for that alkaloid, $p < 0.05$ or 0.01.

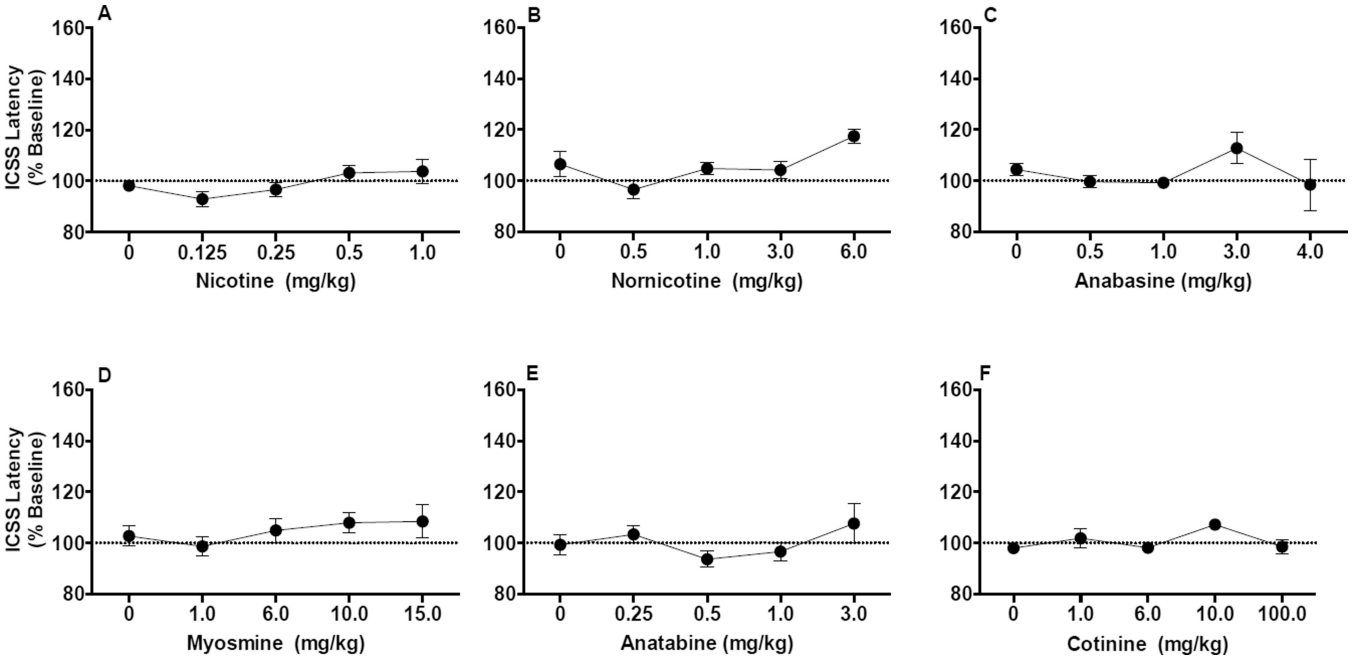

Figure 2.

ICSS response latencies (expressed as percent of baseline, mean ± SEM) following injection of nicotine (A), nornicotine (B), anabasine (C), myosmine (D), anatabine (E), or cotinine (F).