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Development of a novel alcohol and nicotine concurrent access (ANCA) self-administration procedure in baboons

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Abstract

Background.—Self-administration of either alcohol or nicotine under single-access conditions has been studied extensively in laboratory animals. Relatively few studies have examined the co-use of these substances, even though alcohol and nicotine use and abuse commonly co-occur in humans. The objectives of this study were to develop a baboon model of concurrent alcohol and nicotine self-administration, and examine effects of varenicline on alcohol and nicotine co-use.

Methods.—In Experiment 1, five male baboons were trained to self-administer drinks of alcohol (4% w/v) and injections of nicotine (0.032–0.1 mg/kg) under single-access and then concurrent-access conditions, and intake of alcohol (g/kg) and nicotine (mg/kg) was compared under single- and concurrent-access conditions. In Experiment 2, three male baboons self-administered drinks of alcohol (4% w/v) and injections of nicotine (0.056 mg/kg) under concurrent-access conditions. Pretreatment with varenicline (0.32–1.0 mg/kg, s.c.) or an equal volume of its vehicle before concurrent-access sessions was repeated for 5 consecutive days.

Results.—Self-administration of nicotine and alcohol was successfully established under both single- and concurrent-access conditions that produced reliable levels of voluntary alcohol and nicotine intake. Co-self-administration of both drugs produced levels of intake similar to that produced by each drug alone. Varenicline significantly reduced intake of both alcohol and nicotine when compared to the vehicle condition.

Conclusions.—This baboon model provides a valuable tool for further investigation of the behavioral and pharmacological mechanisms involved in co-use of nicotine and alcohol. A single pharmacotherapeutic agent (e.g., varenicline) may be useful in treating nicotine and alcohol co-use.

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Contributors.

EW was responsible for the study concept and design, and monitored the acquisition of animal data. AFH, CMD, and EW assisted with data analysis and interpretation of findings. AFH wrote the first draft of the manuscript, and CMD and EW provided substantive and conceptual feedback on subsequent drafts. All authors contributed to and have approved the final manuscript.

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Keywords

alcohol; baboon; co-use; nicotine; self-administration; varenicline

1. Introduction

Tobacco smoking and heavy alcohol use are leading causes of preventable illness and death in the United States, and are co-occurring problems. Alcohol use disorder is over 10 times more common among smokers than non-smokers (Batel et al., 1995; Marks et al., 1997), and as many as 80% of alcohol-dependent individuals use tobacco or other nicotine products (Romberger and Grant, 2004). Furthermore, individuals who co-use alcohol and nicotine have worse clinical outcomes than individuals who use either drug alone (Dawson, 2000; Friedman et al., 1991). An evaluative review identified the need for research using animal models that mimic human nicotine and alcohol co-use, to gain a better understanding of how these drugs interact and to identify new therapeutic targets (Van Skike et al., 2016).

Several pre-clinical studies on alcohol and nicotine co-use have examined effects of passive (experimenter) administration of one drug on self-administration of the other (Tarren and Bartlett, 2017). Relatively few studies have reported on co-use of alcohol and nicotine in laboratory animals when both alcohol and nicotine were available for self-administration or consumption. Studies to date have been primarily in rodents, and have included concurrent, oral consumption procedures (2- or 3-bottle free-choice method; Marshall et al., 2003); operant self-administration procedures in which alcohol and nicotine were available in combination (Deehan et al., 2015) or concurrently (Lê et al., 2010); combined oral consumption and operant self-administration procedures (Maggio et al., 2018a; Maggio et al., 2018b); and sequential-access procedures where access to alcohol or nicotine was alternated sequentially throughout the session (Lê et al., 2014). These studies demonstrate that reliable co-administration of alcohol and nicotine can be established in laboratory animals.

The first objective of this project was to develop a nonhuman primate (i.e., baboon) model of concurrent alcohol and nicotine self-administration. Nonhuman primates are closer to humans in phylogenetic origin, and are more genetically, physiologically, and behaviorally similar to humans than rodents. Nonhuman primate models provide a critical bridge in the translational research gap between rodents and humans. Of high significance is that metabolism and pharmacokinetic parameters of alcohol, nicotine, and other drugs in nonhuman primates are closely similar to humans (Friedman et al., 1991; Jolivet and Ward, 2005; Ward and Smith, 2004), and such species differences may ultimately affect predictive value for clinical treatment outcomes. As reviewed previously (Matta et al., 2007), there are significant species differences and route differences in the metabolism of nicotine. The half-life of nicotine in plasma in rodents is short (45 min in the rat and 6–7 min in the mouse). In contrast, like humans, the half-life of nicotine in plasma in nonhuman primates is about 2 hours. In addition, nonhuman primates metabolize nicotine primarily to cotinine (70–80%) as humans do (Seaton et al., 1991). Rats metabolize nicotine to form nicotine-N'-oxide as much as they do cotinine and also form 3'-hydroxycotinine due to differences in

predominant cytochrome P450 enzymes (Seaton and Vesell, 1993). Such species differences are important as cotinine is biologically active and has been shown to be involved in nicotine dependence.

The second objective of this project was to examine effects of varenicline on alcohol and nicotine co-self-administration in baboons. Varenicline is an FDA-approved medication for smoking cessation that is under investigation for alcohol use disorder treatment. Varenicline has been shown to reduce nicotine self-administration in rodents (George et al., 2011; O'Connor et al., 2010), and promote smoking cessation in humans (Ebbert et al., 2016). Effects of varenicline on alcohol consumption in rodents (Froehlich et al., 2017), baboons (Kaminski and Weerts, 2014), and humans (de Bejczy et al., 2015; Plebani et al., 2013) have been mixed, indicating that further investigation of varenicline is warranted, especially regarding effects related to alcohol and nicotine co-use.

2. Material and Methods

2.1. Experiment 1: Single- and Concurrent-Access Drug Availability

2.1.1. Subjects and Apparatus—Five adult male baboons (*Papio anubis*), initially weighing 26.6 to 33.5 kg, were individually housed in custom-designed primate cages that also served as the experimental chambers. The baboons were fed standard primate chow adjusted to maintain sufficient caloric intake (e.g., 50–73 kcal/kg), 2 pieces of fresh fruit or vegetables (70–120 g each), and a children's chewable multivitamin daily. Tap water from a drinking spout located on the front of the cage was continuously available 24 hours per day and water intake was recorded daily at the same time each day (8:30 AM). The housing room was maintained under a 12-hour light/dark cycle, with lights on from 6:00 AM to 6:00 PM daily. The facilities were maintained in accordance with USDA and AAALAC standards, and the protocol was approved by the Johns Hopkins University Animal Care and Use Committee.

Baboons were fitted with a tether/harness/vest system that allowed unrestricted movement within the cage (see Figure 1) and surgically implanted with a chronically indwelling intravenous (IV) catheter as described previously (Lukas et al., 1982). The catheter was attached to a custom three-way valve system connected to three separate peristaltic infusion pumps (Model 1201 or Model 66 Harvard Apparatus, Natick, MA). Intravenous solutions (nicotine or saline) were injected into the catheter via one pump and followed by a saline flush into the vein using a second pump. To maintain catheter patency, a third pump continuously infused approximately 250 ml of heparinized saline (5–10 units/ml). The peristaltic pumps, infusion systems, and drug solutions were located on a metal grating that ran above the cage. Baboons were anesthetized every 2–3 weeks with ketamine hydrochloride (preceded by atropine sulfate) to permit cage washing, weighing, physical examinations, and catheter care.

The primate cages were equipped with a bench that ran along one of the side walls and an aluminum intelligence panel that was mounted on the rear wall. The intelligence panel contained two vertically-operated levers (Med Associates model ENV-121) mounted in the lower left quadrant of the panel within easy reach of the baboon when seated on the bench.

Different colored jewel lights (red, blue, or yellow; 1.5 cm diameter) were mounted above each lever. A custom-built drinkometer (Kandota Instruments, Sauk Center, MN) which contained two white and two green lights that surrounded a protruding drink spout was located above the levers and jewel lights in the upper left quadrant of the panel. A 5×5 cm panel with a green light bulb (bay light) was located in the right quadrant of the intelligence panel. Figure 1 shows the configuration of the various components on the intelligence panel. All orally self-administered solutions (i.e., alcohol) were delivered from a calibrated 2000 ml bottle that was positioned on the grating above the cage and connected to the drinkometer. A speaker for delivery of white noise and tones was mounted behind the panel. Experimental control and data collection were accomplished using personal computers with MED Associates Inc. (East Fairfield, VT) software and instrumentation that were connected to the intelligence panel on the outside of the cage.

2.1.2. Drug Self-Administration Procedure—Experimental sessions lasting 6 hours were conducted seven days per week and began at the same time each day. Self-administration of alcohol and nicotine was examined under single- and concurrent-access conditions; self-administration under single-access conditions was established prior to concurrent-access conditions. Baboons were assigned to start with single access to either alcohol (n=3; BV, GG, and HG) or nicotine (n=2; BS and LI). For each drug, self-administration was contingent on lever responses on either the left (alcohol) or right (nicotine) levers, each of which was associated with unique cue lights. Completion of the response requirement on the alcohol lever activated the drinkometer and drinks were delivered upon contact with the drink spout. Completion of the response requirement on the nicotine lever resulted in IV delivery of nicotine. A minimum of 10 sessions were conducted and sessions continued until self-administration was stable based on visual inspection. Details for alcohol and nicotine delivery are provided below.

2.1.2.1. Alcohol (Oral) Self-Administration Procedure: Drinks of alcohol (4% w/v) were available under a fixed-ratio (FR) 3 schedule of reinforcement on the alcohol lever (i.e., three lever responses for access to one “drink” of alcohol from the drinkometer). A concentration of 4% w/v alcohol was selected because it maintains higher rates of operant self-administration than high concentrations (e.g., 8 to 16% w/v) and, as demonstrated in our prior studies in baboons with alcohol drinking experience, it is preferred over water when both are available concurrently (Ator and Griffiths, 1992), and typically produced blood alcohol levels (BALs) that exceeded 0.08% (Holtyn et al., 2014; Kaminski et al., 2008). Alcohol availability was signaled by a 5-second tone, followed by illumination of the cue light above the alcohol lever. Completion of the FR 3 turned off the cue light, activated the drinkometer (signaled by illumination of the lights on the drinkometer), then contact with the drink spout allowed fluid flow for 5 seconds or until spout contact was broken, whichever occurred first. This defined a single “drink” of alcohol. A 30-second timeout, correlated with illumination of the bay light, began after the FR 3 was completed. During timeout, responses were recorded but had no programmed consequence.

2.1.2.2. Nicotine (IV) Self-Administration Procedure: Nicotine infusions (0.032, 0.056, or 0.1 mg/kg/infusion) were available under an FR 3 schedule of reinforcement on the

nicotine lever. The doses of nicotine selected were based on those used in previous studies in baboons (Ator and Griffiths, 1983). Nicotine injection availability was signaled by a 5-second tone, followed by illumination of the cue light above the nicotine lever. Completion of the FR 3 turned off the cue light and an IV infusion of nicotine was delivered over 50 seconds followed by a 0.9% saline flush infusion over 50 seconds during which the bay light was illuminated. This was then followed by a 30-second timeout. During timeout, responses were recorded but had no programmed consequence.

2.1.3. Concurrent-Access Procedure—During concurrent-access conditions, alcohol (4% w/v) and nicotine (0.032, 0.056, or 0.1 mg/kg/infusion) were both available for self-administration. Each drug was available independently, in that responses on the lever for one drug did not affect access to or delivery of the other drug. Nicotine dose order was mixed across baboons.

2.2. Experiment 2: Effects of Varenicline on Concurrent-Access Drug Availability

2.2.1. Subjects, Apparatus, and Self-Administration Procedure—Three of the baboons from Experiment 1 (BV, BS, and GG) were used to examine effects of varenicline on concurrent self-administration of alcohol and nicotine. The procedures for feeding and housing the baboons were identical to those described in Experiment 1. Experimental sessions lasting 6 hours were conducted seven days per week and began at the same time each day. During experimental sessions, alcohol (4% w/v) and nicotine (0.056 mg/kg/injection) were both available for self-administration. We selected the 0.056 mg/kg nicotine dose to test effects of varenicline because it produced reliable self-administration, and total intake exceeded nicotine content of 10 cigarettes. In humans, smoking delivers a dose of about 1 mg nicotine per cigarette, and regular smoking of 10 or more cigarettes per day is strongly associated with nicotine dependence. Drinks of alcohol were available under an FR 3 schedule of reinforcement on the alcohol lever and nicotine injections were available under an FR 3 schedule of reinforcement on the nicotine lever. Responses on the lever for one drug did not affect access to or delivery of the other drug. The experimental cues and stimulus events were identical to those described in Experiment 1.

2.2.2. Varenicline Test Procedures—After self-administration was stable (total intake was within + 20% for 3 consecutive sessions), varenicline (0.32, 0.56, and 1.0 mg/kg) or vehicle was administered via subcutaneous injection for five consecutive days. Drug doses and vehicle were administered 30 minutes before each session and were given in mixed order across baboons. Baseline levels of intake were reestablished for at least 2 weeks and stable before proceeding to the next dosing period (i.e., 2–3-week washout period). Varenicline doses were selected based our prior study in alcohol drinking baboons (Kaminski and Weerts, 2014), doses tested in humans for alcohol (Litten et al., 2013), and therapeutic doses as prescribed for smoking cessation.

2.3. Drugs

Ethyl alcohol (190 Proof; Pharmco-AAPER, Brookville, CT) was diluted with reverse osmosis purified drinking water to a concentration of 4% w/v alcohol. Nicotine hydrogen tartrate (Sigma/Aldrich, St. Louis, MO, and NIDA Drug Supply Program) was dissolved in

0.9% saline and filter sterilized. Varenicline dihydrochloride (0.32, 0.56, and 1.0 mg/kg; Research Triangle Institute, Research Triangle Park, NC) was dissolved in 2 ml of 0.9% saline and administered via subcutaneous injection. Vehicle (saline) was administered using the same volume and route of injection for control conditions. All drug doses were based on the salt.

2.4. Data Analysis

During experimental sessions, the number of lever responses, spout contacts (alcohol delivery), and IV nicotine injections delivered were recorded by the computer program. Alcohol and nicotine intake was defined as the total dose (g/kg alcohol and mg/kg nicotine) consumed/delivered, and was calculated using each baboon's weight and total amount of alcohol consumed orally or nicotine delivered IV. Total water intake was recorded daily at the same time each day in milliliters. For Experiment 1, nicotine and alcohol intake under single- and concurrent-access conditions were compared separately using two-way repeated measures analysis of variance (ANOVA) with condition (single access or concurrent access) and nicotine dose (0.032, 0.056, and 0.1 mg/kg) as factors. For Experiment 2, the grand mean of the three sessions before each chronic-dosing period was used as the baseline for comparison with vehicle and varenicline doses, and the mean of the five sessions during each chronic-dosing period was used for vehicle and varenicline conditions. Effects of chronic administration of varenicline were analyzed separately for alcohol, nicotine, and water intake for each baboon using repeated measures ANOVA with condition (vehicle, 0.32, 0.56, and 1.0 mg/kg varenicline) as a repeated measure. For the repeated measures ANOVAs, the method of Geisser and Greenhouse was used to correct for violations of sphericity. When significant effects were determined, post-hoc Dunnett's *t*-tests were used for pairwise comparisons. For all statistical analyses, a *p*-value of .05 or less was considered significant. Statistical analyses were conducted using GraphPad Prism® 8 software.

3. Results

3.1. Experiment 1

Figure 2 shows total mg/kg of nicotine (mg/kg/injection) delivered and total g/kg alcohol (4% w/v) consumed during single access to nicotine or alcohol. Self-administration of nicotine and alcohol was successfully established under single-access conditions. On average, baboons self-injected 0.35, 0.83, and 1.60 mg/kg nicotine when 0.032, 0.056, and 0.1 mg/kg/nicotine, respectively, was available alone. Baboons drank 0.79 g/kg alcohol, on average, when alcohol was available alone. Nicotine and alcohol intake was stable across sessions for individual baboons.

Figure 3 shows total mg/kg of nicotine (mg/kg/injection) delivered and total g/kg alcohol (4% w/v) consumed during concurrent access to nicotine and alcohol. On average, baboons self-injected 0.41, 0.97, and 1.80 mg/kg nicotine when 0.032, 0.056, and 0.1 mg/kg/nicotine, respectively, was available concurrently with alcohol. Baboons drank between 1.0 to 1.2 g/kg alcohol, on average, when nicotine was available concurrently. Nicotine and alcohol intake was stable across sessions for individual baboons.

Intake of alcohol and nicotine was similar under single- and concurrent-access conditions. Baboons self-injected similar amounts of nicotine when alcohol was unavailable and available; there was no significant interaction between condition (single access versus concurrent access) and dose on nicotine intake [$F(2,16) = 0.09$; $p = .914$], and no significant main effect of condition ($p = .675$). Total nicotine intake increased as the nicotine dose was raised ($p = .013$). Baboons consumed similar amounts of alcohol when nicotine was unavailable and available; there was no significant interaction between condition and dose on alcohol intake [$F(2,16) = 0.51$; $p = .610$], and no significant main effect of condition ($p = .123$). Changing the dose of nicotine that was available for self-administration did not change alcohol intake ($p = .514$).

Figure 4 shows patterns of intake of both alcohol and nicotine for baboons that were repeatedly exposed to the condition in which 4% w/v alcohol and 0.056 mg/kg/injection nicotine were concurrently available. Baboons continued to self-administer alcohol and nicotine over repeated exposures. The conditions shown in Figure 4 were not run to stability, but were separated by days on which cage washing, physical examinations and weighing of the baboons, and catheter care occurred.

3.2. Experiment 2

During baseline sessions, stable and reliable self-administration of both nicotine (0.056 mg/kg/injection) and alcohol (4% w/v) was observed in all baboons. The grand mean (+ SEM) nicotine intake was 1.48 (0.11) mg/kg and alcohol intake was 1.55 (0.11) g/kg. Figure 5 shows effects of chronic administration of varenicline on concurrent nicotine and alcohol self-administration for individual baboons. Varenicline significantly decreased both nicotine and alcohol self-administration in each baboon (all $F_s = 6.99$ – 46.94 ; $p_s < .05$). Relative to vehicle, 1.0 mg/kg varenicline significantly reduced nicotine and alcohol self-administration in all of the baboons; there was individual variability in whether the lower doses of varenicline also decreased nicotine and alcohol self-administration. Water was continuously and freely available during the session; varenicline did not significantly change total water intake in each baboon when compared to vehicle (see supplementary Figure 1s; all $F_s = 1.62$ – 4.75 ; $p_s > .05$).

4. Discussion

The present study developed a nonhuman primate model of concurrent nicotine and alcohol self-administration, and sought to examine intake of the two drugs when they were available concurrently and alone. Self-administration of nicotine and alcohol was successfully established in baboons under both single- and concurrent-access conditions that produced pharmacologically relevant levels of voluntary IV nicotine and oral alcohol intake. In humans, smoking delivers a dose of about 1 mg nicotine per cigarette (Benowitz and Jacob III, 1984), and regular smoking of 10 or more cigarettes per day is strongly associated with nicotine dependence. When 0.056 mg/kg/injection nicotine was available for self-administration in the present study, nicotine intake under single-access (~0.83 mg/kg nicotine) and concurrent-access (~0.97 mg/kg nicotine) conditions exceeded the nicotine content of 10 cigarettes. Alcohol intake under single-access (~0.79 g/kg alcohol) and

concurrent-access (~1.1 g/kg alcohol) conditions was comparable to that seen in previous studies in which baboons self-administered sufficient alcohol (0.8–1.0 g/kg alcohol) to reach blood alcohol levels exceeding 0.08% (Holtyn et al., 2014; Kaminski et al., 2008). In humans, a 0.08% blood alcohol level exceeds the legal limit for driving while intoxicated in the United States. Given that drinking and smoking commonly co-occur in humans, this baboon model provides a valuable tool for further investigation of the behavioral and pharmacological mechanisms involved in co-use of nicotine and alcohol.

Co-self-administration of both drugs produced levels of intake similar to that produced by each drug alone. In addition, with repeated and chronic exposure to concurrent alcohol and nicotine self-administration, intake of both drugs persisted. This is consistent with findings from some pre-clinical examinations of co-use of alcohol and nicotine in rodents. In two studies, when both alcohol and nicotine were available for oral consumption, rats consumed the same amounts of nicotine and alcohol regardless of whether offered individually or together (Deehan et al., 2015; Marshall et al., 2003). Other studies in rodents have shown concurrent access to alcohol to decrease (Funk et al., 2016; Lê et al., 2010) and increase (Maggio et al., 2018a) self-administration of nicotine; and concurrent access to nicotine to decrease (Funk et al., 2016) and increase (Lê et al., 2014) self-administration of alcohol. In humans, both nicotine and alcohol have been shown to alter the physiological and subjective effects of each other in terms of craving, reinforcement, and self-administration (McKee et al., 2008; Ray et al., 2007). Continued attention to the ways in which nicotine and alcohol co-use may modify intake of one or both of the drugs is warranted.

This study examined effects of varenicline on concurrent nicotine and alcohol self-administration in our baboon model of co-use. Varenicline binds to multiple nicotinic acetylcholine receptors (nAChRs), acting as a full agonist at $\alpha 7$ and $\alpha 3\beta 4$, and a partial agonist at $\alpha 4\beta 2$, $\alpha 3\beta 2$, and $\alpha 6\beta 2$, with the highest affinity for the $\alpha 4\beta 2$ subtype (Grady et al., 2010). Nicotinic acetylcholine receptors have been proposed to be the common biological target of nicotine and alcohol, although the mechanisms by which nAChRs modulate drinking and smoking behaviors may differ since nicotine acts as a direct agonist at nAChRs, while alcohol does not (Feduccia et al., 2012). In the present study, varenicline significantly reduced intake of both nicotine and alcohol, suggesting efficacy of varenicline for reduction of alcohol and nicotine co-use. A preclinical study using a rodent model of alcohol and nicotine co-use also showed that varenicline significantly decreased both nicotine and alcohol self-administration during concurrent access (Cippitelli et al., 2015), although others showed significant reductions in nicotine, but not alcohol, self-administration (Funk et al., 2016; Maggio et al., 2018a; Maggio et al., 2018b; Scuppa et al., 2015). The present results also are consistent with a prior study in baboons in which varenicline produced modest decreases in alcohol intake in a 2-hour alcohol drinking model (Kaminski and Weerts, 2014). In humans, two randomized, placebo-controlled clinical trials have examined effects of varenicline in both cigarette smokers and non-smokers (N=200; Litten et al., 2013) and smokers (N=131; O'Malley et al., 2018) with alcohol use disorders. Varenicline (1 mg twice daily) significantly reduced heavy alcohol drinking in the intent-to-treat sample in one study (Litten et al., 2013) but not the other (O'Malley et al., 2018); cigarette smoking was significantly reduced among smokers who received varenicline in

both studies (Litten et al., 2013; O'Malley et al., 2018). However, varenicline treatment outcomes for alcohol drinking and cigarette smoking may differ by sex (Bold et al., 2019).

A few limitations should be noted. First, the present study did not examine the selectivity of varenicline effects, such as by examining effects on self-administration of a non-drug reinforcer (Czoty et al., 2016; Haney and Spealman, 2008). Treatment with varenicline did not reduce total water intake, providing some evidence of selective effects. It is worth noting that the selectivity of varenicline effects may depend on the experimental arrangement. For example, varenicline has been shown to selectively reduce alcohol-maintained responding when alcohol and an alternative reinforcer are available alone or sequentially, but not when both are available concurrently (Ginsburg and Lamb, 2014a, b). Second, this study showed that varenicline significantly reduced intake of alcohol and nicotine when they were available concurrently; it did not examine varenicline effects under single-access conditions. However, effects of varenicline on alcohol self-administration alone and nicotine self-administration alone have been explored previously (Funk et al., 2016; Kaminski and Weerts, 2014; Steensland et al., 2007; Wouda et al., 2011).

In sum, the present study developed a nonhuman primate model of concurrent alcohol and nicotine self-administration, and examined effects of varenicline on co-use of alcohol and nicotine. Testing in nonhuman primates – which metabolize nicotine, alcohol, and other drugs similarly to humans and self-administer both drugs concurrently – can increase understanding of how these drugs interact and help identify optimal treatment conditions for new therapeutic targets in people who use both alcohol and nicotine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Co-self-administration of alcohol and nicotine was established in baboons
- Alcohol and nicotine intake was similar during single and concurrent access
- Varenicline reduced co-self-administration of both alcohol and nicotine

Figure 1.

Depiction of the apparatus used for self-administration of intravenous (IV) nicotine and oral alcohol in baboons. The figure shows the baboon vest and tether system for IV catheters, which is connected to a liquid swivel and drug supply above the baboon cage. The figure also shows the intelligence panel, which is mounted on the back of the cage, and contains the alcohol drinkometer, the stimulus lights (jewel lights and bay light), and response levers.

Single Access

Figure 2.

Total milligrams per kilogram (mg/kg) of 0.032 to 0.1 mg/kg/injection nicotine administered and total grams per kilogram (g/kg) of 4% w/v alcohol consumed across 10 consecutive days in baboons (n=5). Data shown are the grand means (+SEM) from the daily single-access sessions in which only nicotine was available for intravenous self-administration (A) and only alcohol was available for oral self-administration (B).

Figure 3.

Total milligrams per kilogram (mg/kg) of 0.032 to 0.1 mg/kg/injection nicotine administered and total grams per kilogram (g/kg) of 4% w/v alcohol consumed across 10 consecutive days in baboons (n=5). Data shown are the grand means (+SEM) from the daily sessions in which both nicotine and alcohol were available concurrently (A-C).

Figure 4.

Total milligrams per kilogram (mg/kg) of nicotine administered (0.056 mg/kg/injection) and total grams per kilogram (g/kg) of alcohol consumed (4% w/v) when nicotine and alcohol were available concurrently. Data shown are consecutive days of intake for each repeated, chronic exposure to the concurrent access condition for the three baboons (designated GG, BV, and BS) in Experiment 2.

Figure 5.

Effects of chronic (5 day) administration of vehicle (Veh) or varenicline (0.32–1.0 mg/kg) on total milligrams per kilogram (mg/kg) of nicotine administered (0.056 mg/kg/injection) and total grams per kilogram (g/kg) of alcohol consumed (4% w/v) when nicotine and alcohol were available concurrently in three baboons (designated GG, BV, and BS). Baseline (BL) includes intake from the three days prior to vehicle or varenicline dosing conditions. Data shown are means (+SEM) from the daily sessions for individual baboons. * and + indicate a significant difference compared to vehicle (* $p < .05$, ** $p < .01$, and *** $p < .001$ for nicotine conditions and + $p < .05$ and ++ $p < .01$ for alcohol conditions).