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Effects of the nicotinic acetylcholine receptor antagonist mecamylamine on the discriminative stimulus effects of cocaine in male rhesus monkeys

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Abstract

Preclinical drug discrimination procedures have been useful in understanding the pharmacological mechanisms of the subjective-like effects of abused drugs. Converging lines of evidence from neurochemical and behavioral studies implicate a potential role of nicotinic acetylcholine (nACh) receptors in the abuse-related effects of cocaine. The aim of the present study was to determine the effects of the nACh receptor antagonist mecamylamine on the discriminative stimulus effects of cocaine in nonhuman primates. The effects of mecamylamine on the cocaine-like discriminative stimulus effects of nicotine were also examined. Male rhesus monkeys (n=5) were trained to discriminate 0.32 mg/kg, IM cocaine from saline in a two-key food-reinforced discrimination procedure. Initially, potency and time course of cocaine-like discriminative stimulus effects were determined for nicotine and mecamylamine alone. Test sessions were then conducted examining the effects of mecamylamine on cocaine or the cocaine-like discriminative stimulus effects of nicotine. Curiously, both nicotine and mecamylamine produced partial cocaine-like discriminative stimulus effects. Mecamylamine did not significantly alter the discriminative stimulus effects of cocaine up to doses that significantly decreased rates of operant responding. Mecamylamine and nicotine combinations were not different than saline. These results confirm previous nonhuman primate studies of partial substitution with nicotine and extend these findings with mecamylamine. Furthermore, these results extend previous results in rats suggesting cocaine may have nACh receptor antagonist properties.

Keywords

cocaine; methamphetamine; nicotine; mecamylamine; rhesus monkey

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Introduction

Discrimination procedures have been useful over the past 70 years in furthering our understanding of the pharmacological determinants of the subjective-like effects of abused drugs. A discriminative stimulus is operationally defined as any stimulus that varies with the availability of a reinforcing consequent stimulus (Schuster & Balster, 1977). Drugs can be explicitly trained as discriminative stimuli and these preclinical drug discrimination procedures have been useful in understanding the pharmacological determinants of a drug's subjective-like effects and ultimately an indication of the abuse potential (Fischman & Foltin, 1991; Preston & Bigelow, 1991). Moreover, because drug discrimination procedures can be readily trained across different species from rodents to nonhuman primates to humans, the procedures allow for a high degree of translatability between research findings.

There are several lines of neurochemical and behavioral evidence suggesting a role of nicotinic acetylcholine (nACh) receptors in the abuse-related effects of cocaine. Optogenetic stimulation of cholinergic interneurons in rats increases extracellular dopamine levels in the nucleus accumbens (Cachope et al., 2012) and dopamine release in this brain region is thought to be important in mediating the subjective effects of cocaine (Wise, 2008). Furthermore, intra- accumbens administration of the non-selective and non-competitive nACh receptor antagonist mecamylamine blocked cocaine-induced increases in extracellular DA levels in rats (Zanetti, Picciotto, & Zoli, 2007). Moreover, in monkeys, mecamylamine increased dopamine transporter availability as measured using positron emission tomography suggesting mecamylamine decreased extracellular dopamine levels (Tsukada et al., 2001). Regarding behavioral evidence, mecamylamine pretreatment reduced cue-induced cocaine craving in cocaine and nicotine- dependent individuals (Reid, Mickalian, Delucchi, & Berger, 1999) and blocked cocaine-induced conditioned place preference in mice (Zachariou et al., 2001). However, mecamylamine failed to block the discriminative stimulus effects of cocaine in rats (Cunningham, Polston, Jany, Segert, & Miller, 2006; Desai, Barber, & Terry, 2003) and enhanced the discriminative stimulus effects of cocaine in monkeys (Gould, Czoty, Nader, & Nader, 2011). Furthermore, nicotine and cocaine produce asymmetrical cross-generalization, such that nicotine fully substituted for the discriminative stimulus effects of cocaine (Desai et al., 2003), but cocaine did not substitute, or only partially substituted, for the discriminative stimulus effects of nicotine (Desai et al., 2003; Mansbach, Rovetti, & Freedland, 1998; Stolerman, Garcha, Pratt, & Kumar, 1984). In contrast, nicotine substituted in one of three monkeys trained to discriminate cocaine (Mello & Newman, 2011) and cocaine only partially substituted in monkeys trained to discriminate nicotine (Cunningham, Javors, & McMahon, 2012). When nicotine was given as a pretreatment to cocaine, nicotine produced leftward shifts in the cocaine discriminative stimulus dose-effect function compared to cocaine alone (Gould et al., 2011; Mello & Newman, 2011). Overall, this body of literature suggests two main findings. First, this literature suggests that activation of nACh receptors with nicotine is sufficient to produce cocaine-like discriminative stimulus effects in rats, but probably not nonhuman primates. These results suggest potential species differences regarding the behavioral effects of nicotinic compounds. Second, the results from Gould et al. (2011) that both the nACh receptor antagonist mecamylamine and the nACh receptor agonist nicotine produced

qualitatively similar enhancement of the discriminative stimulus effects of cocaine warrants further investigation and clarification.

The aim of the present study was to determine whether nACh receptors were necessary for the discriminative stimulus effects of cocaine in male rhesus monkeys. To test this aim, the effects of the nACh receptor antagonist mecamylamine alone and in combination with cocaine were determined. As a control, we also determined mecamylamine effects on the cocaine-like discriminative stimulus effects of nicotine. We hypothesized that nACh receptors would be necessary for the discriminative stimulus effects of cocaine because cocaine-induced increases in dopamine are impulse-dependent. These expected results would suggest a role of the nicotinic acetylcholine system in the subjective-like effects of cocaine. A secondary aim of the present study was to extend previous results in nonhuman primates by determining the time course of discriminative stimulus effects of all test compounds alone and in combination with mecamylamine using a novel procedure that allows for within-session time course discriminative stimulus determination (Banks, Blough, Fennell, Snyder, & Negus, 2013). We were particularly interested in time course studies in an attempt to clarify and expand upon the previous nonhuman primates studies that have only used dose-effect procedures to investigate nACh receptor agonist or antagonist interactions with cocaine.

Methods

Animals

Studies were conducted in 5 adult male rhesus monkeys (*Macaca mulatta*) weighing between 9 and 13 kg. Monkeys were maintained on a diet of fresh fruit and food biscuits (Lab Diet High Protein Monkey Biscuits, PMI Feeds, Inc., St. Louis, MO) provided in the afternoon after the operant behavioral session. In addition, monkeys could earn 1-gm banana-flavored pellets (5TUR Grain-based Precision Primate Pellets, Test Diets, Richmond, IL) during daily experimental sessions. Water was continuously available in the home cage. A 12 hr light-dark cycle was in effect (lights on from 7AM to 7PM). Environmental enrichment consisting of foraging boards, novel treats, movies or radio was also provided in the afternoons after the behavioral session. All monkeys had prior exposure to monoaminergic (Banks, Blough, Fennell, et al., 2013) and opioidergic compounds (unpublished results). The facility was licensed both by the United States Department of Agriculture and the Association for Assessment and Accreditation of Laboratory Animal Care. The Institutional Animal Care and Use Committee approved all protocols.

Apparatus

Experimental sessions were conducted 5 days/week in each monkey's home cage as described previously (Banks, Blough, Fennell, et al., 2013). The front door of the cage was equipped with an operant response panel that included three square response keys arranged horizontally that could be transilluminated red or green; only the left and right keys were used in the present experiments. Attached to the operant panel was a pellet dispenser (Med Associates, ENV-203-1000, St. Albans, VT) for delivery of 1-gram pellets. Operation of the

operant panels and data collection was accomplished computers and with software purchased from Med Associates.

Discrimination Training

Monkeys were trained to discriminate intramuscular (IM) 0.32 mg/kg cocaine from saline in a two-key, food-reinforced drug discrimination procedure. Daily discrimination training sessions were composed of multiple response components. Each component consisted of a 5-min response period during which the right and left response keys were transilluminated red or green, respectively, and monkeys could earn up to 10 food pellets by responding under a fixed-ratio (FR) 30 schedule of food presentation. Training sessions were composed of three response components presented at 2h intervals, and either saline or 0.32 mg/kg cocaine was administered IM 15 min prior to the start of each component. Thus, on training days, monkeys would receive a sequence of saline (S) and cocaine (C) injections in the order SSS, SSC, SCS, CSS, SCC, CSC, or CCC, and training sequences were randomly presented. Following administration of saline or no injection, only responding on the green key (the saline-appropriate key) produced food, whereas following administration of 0.32 mg/kg cocaine, only responding on the red key (the cocaine-appropriate key) produced food. Responses on the inappropriate key reset the FR requirement on the appropriate key. The criterion for accurate discrimination was 85% injection-appropriate responding before delivery of the first reinforcer, 90% injection-appropriate responding for the entire component, and response rates 0.1 responses/s (sufficient to earn at least one pellet) for all components during 7 of 8 consecutive sessions.

Discrimination Testing

Time course test sessions were identical to training sessions except (1) completing the response requirement on either key produced food and (2) 5-min response components began 10, 30, 56, 100, 180, and 300 min after the last injection to assess the time course of drug effects. (–)-Cocaine (0.1 – 1.0 mg/kg, IM), (–)-nicotine (0.1 – 1.0 mg/kg, IM), ketamine (0.32 – 1.0 mg/kg, IM), and (±)-mecamylamine (0.32 – 1.8 mg/kg, IM) were tested up to doses that either produced full substitution for the training dose of cocaine or that significantly decreased rates of operant responding. Test sessions were separated by at least 3 days, and were usually conducted on Tuesdays and Fridays, with training sessions conducted on other weekdays. Test sessions were conducted only if performance during the previous two training sessions met the criteria for accurate discrimination described above. All doses from one test drug were determined in one monkey before testing the next drug. Drug doses were counterbalanced between monkeys. In general, cocaine studies were conducted first, then nicotine studies, and finally the ketamine studies. Furthermore dose-effect functions for cocaine, nicotine, ketamine and mecamylamine alone were double determined. Test sessions examining the effects of mecamylamine pretreatment before cocaine or nicotine were single determinations.

In addition to the time course test sessions, cumulative cocaine dosing test sessions were conducted and were identical to training sessions except (1) completing the response requirement on either key produced food and (2) cocaine or nicotine were administered using a cumulative dosing procedure in 3 male rhesus monkeys. In this procedure,

increasing doses of cocaine or nicotine were administered IM at the beginning of each successive 20-min component (15 min timeout and 5 min response period), and each successive cocaine or nicotine dose increased the total cumulative cocaine or nicotine dose by 0.5 log units. Mecamylamine (1.0 – 1.8 mg/kg, IM) was given as a 60 min pretreatment to the start of this cumulative dosing procedure based on results from the time course studies above. Dose-effect functions of cocaine and nicotine alone were double determined and these test sessions were conducted before and after the mecamylamine pretreatment studies. Mecamylamine pretreatment test sessions were single determinations and mecamylamine pretreatment doses were counterbalanced between monkeys.

Data Analysis

The primary dependent measures were (1) percent cocaine-appropriate responding (%CAR) {defined as (number of responses on the cocaine-associated key divided by the total number of responses on both the cocaine-and saline-associated keys)*100}, and (2) rates of responding for each component. These dependent measures were then plotted as a function of time after cocaine, nicotine, or saline administration or as a function of the cumulative unit drug dose administered. Both %CAR and response rate measures were analyzed using a univariate mixed-model analysis with test drug dose or mecamylamine dose and time as the main factors. Univariate analysis was utilized to accommodate missing data points for the % CAR dependent measures as a result of rate-decreasing effects and we have previously used this analysis (Banks, Blough, & Negus, 2013). A significant main effect was followed by the Tukey HSD multiple comparisons post-hoc test. The criterion for significance was set *a priori* at the 95% level of confidence ($p < 0.05$).

Drugs

(–)-Cocaine HCl and (±)-mecamylamine HCl were generously provided by the National Institute on Drug Abuse Drug Supply Program (National Institutes of Health, Bethesda, MD) and these compounds were dissolved in sterile saline. Ketamine HCl (100 mg/mL) was obtained from a commercial supplier (KetaVed™, Vedco Inc, Saint Joseph, MO). (–)-Nicotine hydrogen tartrate salt (Sigma Aldrich, St. Louis, MO) was dissolved in sterile saline and sodium hydroxide was added to reach a stable pH of approximately 7. Cocaine, ketamine, and mecamylamine doses were expressed as the salt forms listed above whereas nicotine doses were expressed as the free base by multiplying the bitartrate dose by 0.325 (Matta et al., 2007).

Results

Time course of the discriminative stimulus effects of cocaine, nicotine, and ketamine

During the average of all training days that preceded test days, monkeys responded almost exclusively on the cocaine-appropriate key during cocaine training components (mean $\pm$ SEM %CAR: 99.91 ± 0.07) and almost exclusively on the saline-appropriate key during saline training components (99.62 ± 0.2). Mean response rates ($\pm$ SEM) were $2.85 (\pm 0.35)$ and $2.38 (\pm 0.35)$ responses per second during the cocaine and saline training components, respectively.

Figure 1 shows the potency and time course of saline, (A) cocaine and (B) nicotine alone. Saline administration produced 10% CAR at all time points and had no significant effect on rates of responding throughout the test period in all test sessions. In contrast, the cocaine training dose (0.32 mg/kg) produced full cocaine discriminative stimulus effects, defined as 90% CAR at any time point, in all 5 monkeys. Full substitution occurred in 2 monkeys after 0.1 mg/kg cocaine. In addition, (cocaine dose: ($F_{3,12} = 55.4, p < 0.05$); cocaine dose x time: ($F_{15,56} = 13.5, p < 0.05$)) post-hoc analysis revealed that 0.32 and 1.0 mg/kg cocaine doses were significantly different from saline at 10 and 30 min and only the 1.0 mg/kg cocaine dose was different from saline at 56 min. For nicotine, full substitution was produced in 2 monkeys after 1.0 mg/kg. Univariate analysis demonstrated no significant cocaine-like discriminative stimulus effects. Ketamine (data not shown) was tested as a negative control and did not produce any significant cocaine-like discriminative stimulus effects when analyzed using univariate analysis, but 1.0 mg/kg ketamine did produce full substitution for cocaine in a single monkey.

Figure 1 also shows the effects of (C) cocaine and (D) nicotine on rates of operant responding. For cocaine, post-hoc analysis following univariate analysis (cocaine dose: ($F_{3,12} = 5.0, p < 0.05$); cocaine dose x time: ($F_{15,60} = 2.3, p < 0.05$)) revealed that 1.0 mg/kg cocaine significantly decreased rates of operant responding compared to saline. For nicotine, post-hoc analysis following univariate analysis (nicotine dose: ($F_{3,12} = 1.9, p < 0.05$); nicotine dose x time: ($F_{15,60} = 6.7, p < 0.05$)) revealed that 1.0 mg/kg nicotine significantly decreased rates of operant responding at 10 and 30 min. For ketamine (data not shown), post-hoc analysis following univariate analysis (ketamine dose x time: ($F_{10,40} = 2.3, p < 0.05$)) revealed that 1.0 mg/kg ketamine significantly decreases rates of operant responding at 10 min.

Time course of the discriminative stimulus effects of mecamylamine

Figure 2A shows the dose- effect and time course of the discriminative stimulus effects of mecamylamine given as a 15 min. pretreatment to saline. Full substitution (90% CAR at any time point) for the discriminative stimulus effects of cocaine was produced in 1 monkey after 1.0 mg/kg and 2 monkeys after 1.8 mg/kg. Post-hoc analysis (mecamylamine dose: ($F_{3,12} = 5.8, p < 0.05$)) revealed that 1.8 mg/kg mecamylamine produced cocaine-like discriminative stimulus effects that were significantly different from saline at 56 and 100 min post-saline administration. Figure 2B shows the effects of mecamylamine on rates of operant responding. Post-hoc analysis following univariate analysis (time: ($F_{5,20} = 13.9, p < 0.05$); mecamylamine dose: ($F_{3,12} = 5.0, p < 0.05$)) revealed that 1.8 mg/kg mecamylamine significantly decreased rates of operant responding from 56 to 180 min post- saline administration.

Effects of mecamylamine pretreatment on the discriminative stimulus effects of cocaine and nicotine

Figure 3 shows the effects of mecamylamine (0.32 – 1.8 mg/kg, IM) on the discriminative stimulus effects of 0.32 mg/kg cocaine (A) and 1.0 mg/kg nicotine (B). The unit cocaine dose selected for these mecamylamine interaction studies was the lowest cocaine dose to produce full substitution. The nicotine dose selected was the lowest nicotine dose to produce

any behavioral effect (i.e. rate-decreasing effects) because nicotine failed to produce significant cocaine-like stimulus effects. If nicotine-induced rate-decreasing effects were mediated by nACh receptors, then mecamylamine should antagonize these nicotine effects. For cocaine, univariate analysis demonstrated a main effect of mecamylamine dose only ($F_{3,12} = 3.0, p < 0.05$) and post-hoc analysis failed to reveal any significant effect of mecamylamine on the discriminative stimulus effects of cocaine. After 0.32 mg/kg mecamylamine pretreatment, cocaine produced full substitution in 4 out of 5 monkeys. After 1.0 mg/kg mecamylamine, cocaine produced full substitution in 2 out of 5 monkeys. After 1.8 mg/kg mecamylamine, cocaine produced full substitution in all 5 monkeys. For nicotine, univariate analysis demonstrated no significant effects. After 0.32 mg/kg mecamylamine pretreatment, nicotine produced full substitution in the one monkey that nicotine alone produced full substitution; whereas, after 1.0 and 1.8 mg/kg mecamylamine, nicotine did not produce full substitution in any monkey.

Figure 3 also shows the effects of mecamylamine pretreatment on rates of operant responding after cocaine (C) and nicotine (D) administration. For cocaine, post-hoc analysis following univariate analysis (mecamylamine dose: ($F_{3,12} = 8.6, p < 0.05$)) revealed that pretreatment with 1.8 mg/kg mecamylamine significantly decreased rates of operant responding compared to cocaine alone from 30–100 min and also at 300 min. For nicotine, post-hoc analysis following univariate analysis (time: ($F_{5,20} = 3.4, p < 0.05$); mecamylamine dose x time: ($F_{15,60} = 2.6, p < 0.05$)) revealed that pretreatment with 1.8 mg/kg mecamylamine significantly decreased rates of operant responding compared to nicotine alone at 100 and 180 min post nicotine administration. Furthermore, pretreatment with 0.32 mg/kg mecamylamine attenuated the rate-decreasing effects produced by 1.0 mg/kg nicotine at 30 min post nicotine administration.

Figure 4 shows effects of mecamylamine (1.0 – 1.8 mg/kg) on the cocaine-like discriminative stimulus effects of cocaine (A) or nicotine (B) under the cumulative dosing procedure in 3 monkeys. Cocaine produced a dose-dependent increase in % CAR whereas cumulative nicotine doses produced no cocaine-like effects. Univariate analysis demonstrated no significant main effects of cocaine or nicotine dose or of mecamylamine pretreatment.

Discussion

This study determined effects of the non-selective and non-competitive nACh receptor antagonist mecamylamine on the discriminative stimulus effects of cocaine. There were two main findings. First, mecamylamine produced dose- and time-dependent substitution for the discriminative stimulus effects of cocaine, but only at a dose that also significantly decreased rates of operant responding. These behavioral results suggest that cocaine might have nACh receptor antagonist properties because nACh receptor antagonism was sufficient to produce partial cocaine-like discriminative stimulus effects. Second, mecamylamine failed to significantly alter the discriminative stimulus effects of cocaine. These results suggest nACh receptors are not necessary for the discriminative stimulus effects of cocaine.

Consistent with previously published studies in nonhuman primates examining the cocaine-like discriminative stimulus effects of nicotine (Gould et al., 2011; Mello & Newman, 2011) and the nicotine-like discriminative stimulus effects of cocaine (Cunningham et al., 2012), nicotine did not produce significant cocaine-like discriminative stimulus effects and nicotine effects were individually specific. Furthermore, consistent with previous results from our laboratory, the N-methyl D-aspartate antagonist ketamine also failed to produce cocaine-like discriminative stimulus effects (Banks, Blough, Fennell, et al., 2013). Finally, mecamylamine produced a partial attenuation of the rate-decreasing effects produced by nicotine in the present time course studies. The results of the present study are consistent with previous studies in squirrel monkeys determining nicotine effects on schedule-controlled responding maintained by food presentation or stimulus shock termination and the effects of mecamylamine (Goldberg & Spealman, 1983; Spealman, Goldberg, & Gardner, 1981). These expected results provided the experimental framework for the subsequent interaction studies with mecamylamine.

In the present study, mecamylamine pretreatment did not significantly alter the discriminative stimulus effects of cocaine consistent with previous results in rodents (Desai et al., 2003; Gatch, Flores, & Forster, 2008). At first glance, the present results with cocaine and mecamylamine may appear in contrast to those of Gould et al. (2011) insofar as mecamylamine enhanced the discriminative stimulus effects of cocaine. However, the pretreatment time of mecamylamine in Gould et al. (2011) was 60 min, whereas the mecamylamine pretreatment time in the present study was 15 min for the time course studies. In the present study, mecamylamine produced peak cocaine-like effects between 56 and 100 min after saline administration or 71 to 115 min after mecamylamine administration. Thus, one alternative explanation for the mecamylamine-induced enhancement reported in Gould et al. (2011) might be related to the time course of mecamylamine effects alone in the discrimination procedure. To test this alternative explanation, we administered mecamylamine as a 60 min pretreatment before cumulative doses of cocaine. Although not statistically significant, the results of were qualitatively similar to the results of Gould et al. (2011) suggesting the enhanced cocaine-like discriminative stimulus effects in the Gould study were mostly likely due to mecamylamine alone.

Although the substitution profile of mecamylamine in the present study was unexpected, data in the literature offer clues regarding potential mechanisms. In vitro binding studies demonstrate that cocaine has low micromolar affinity for inhibiting nACh receptors (Francis, Cheng, Weiland, & Oswald, 2001; Francis, Vazquez, Papke, & Oswald, 2000; Hennings, Kiss, De Oliveira, Toth, & Vizi, 1999). Furthermore, previous rodent studies have demonstrated nicotinic antagonist effects of cocaine and cocaine analogs in behavioral assays and concluded these effects were unrelated to the compounds affinity for the monoamine transporters (Damaj, Slemmer, Carroll, & Martin, 1999). Consistent with this hypothesis that cocaine has nACh receptor antagonist properties, cocaine produced a rightward shift of the nicotine discriminative stimulus dose-response function in nonhuman primates (Cunningham et al., 2012) and Gould et al. (2011) also reported mecamylamine produced partial substitution for the discriminative stimulus effects of cocaine in one out of three monkeys. Lastly, the mecamylamine dose (1.8 mg/kg) that produced significant

cocaine-like discriminative stimulus effects in the present study was higher than mecamlamine doses that were sufficient to shift the nicotine discriminative stimulus dose-effect function to the right (Cunningham et al., 2012) in nicotine-trained monkeys. These results would also be consistent with cocaine having nACh receptor antagonist properties such that higher mecamlamine doses were necessary to produce cocaine-like stimulus effects than were necessary to block nicotine stimulus effects. Overall, these results suggest that cocaine may have nicotinic antagonist properties that would explain the substitution profile of mecamlamine in the present study.

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References

- Banks, Matthew L.; Blough Bruce, E.; Fennell, Timothy R.; Snyder, Rodney W.; Stevens, Negus, S. Role of phenmetrazine as an active metabolite of phendimetrazine: Evidence from studies of drug discrimination and pharmacokinetics in rhesus monkeys. *Drug Alcohol Depend.* 2013; 130(1–3): 158–166. <http://dx.doi.org/10.1016/j.drugalcdep.2012.10.026>. [PubMed: 23211394]
- Banks, Matthew L.; Blough, Bruce E.; Negus, S Stevens. Effects of 14-day treatment with the schedule III anorectic phendimetrazine on choice between cocaine and food in rhesus monkeys. *Drug Alcohol Depend.* 2013; 131(3):204–213. doi: <http://dx.doi.org/10.1016/j.drugalcdep.2013.05.005>. [PubMed: 23726979]
- Cachope, Roger; Mateo, Yolanda; Mathur, Brian N.; Irving, James; Wang, Hui-Ling; Morales, Marisela; Cheer, Joseph F. Selective Activation of Cholinergic Interneurons Enhances Accumbal Phasic Dopamine Release: Setting the Tone for Reward Processing. *Cell Reports.* 2012; 2(1):33–41. doi: <http://dx.doi.org/10.1016/j.celrep.2012.05.011>. [PubMed: 22840394]
- Cunningham CS, Javors MA, McMahon LR. Pharmacologic characterization of a nicotine-discriminative stimulus in rhesus monkeys. *J Pharmacol Exp Ther.* 2012; 341(3):840–849. jpet. 112.193078. [PubMed: 22438471]
- Cunningham CS, Polston JE, Jany JR, Segert IL, Miller DK. Interaction of lobeline and nicotinic receptor ligands with the discriminative stimulus properties of cocaine and amphetamine. *Drug Alcohol Depend.* 2006; 84(3):211–222. S0376- 8716(06)00039-1. [PubMed: 16500038]
- Damaj MI, Slemmer JE, Carroll FI, Martin BR. Pharmacological Characterization of Nicotine's Interaction with Cocaine and Cocaine Analogs. *J Pharmacol Exp Ther.* 1999; 289(3):1229–1236. [PubMed: 10336510]
- Desai RI, Barber DJ, Terry P. Dopaminergic and cholinergic involvement in the discriminative stimulus effects of nicotine and cocaine in rats. *Psychopharmacology.* 2003; 167(4):335–343.10.1007/s00213-003-1426-x [PubMed: 12684733]
- Fischman MW, Foltin RW. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *Br J Addict.* 1991; 86(12):1563–1570. [PubMed: 1786488]
- Francis, Michael M.; Cheng, Elaine Y.; Weiland, Gregory A.; Oswald, Robert E. Specific Activation of the $\alpha 7$ Nicotinic Acetylcholine Receptor by a Quaternary Analog of Cocaine. *Mol Pharmacol.* 2001; 60(1):71–79.10.1124/mol.60.1.71 [PubMed: 11408602]
- Francis, Michael M.; Vazquez, Raymond W.; Papke, Roger L.; Oswald, Robert E. Subtype-Selective Inhibition of Neuronal Nicotinic Acetylcholine Receptors by Cocaine Is Determined by the $\alpha 4$ and $\beta 4$ Subunits. *Mol Pharmacol.* 2000; 58(1):109–119.10.1124/mol.58.1.109 [PubMed: 10860932]
- Gatch MB, Flores E, Forster MJ. Nicotine and methamphetamine share discriminative stimulus effects. *Drug Alcohol Depend.* 2008; 93(1–2):63–71. S0376-8716(07)00361-4. [PubMed: 17961933]

- Goldberg SR, Spealman RD. Suppression of behavior by intravenous injections of nicotine or by electric shocks in squirrel monkeys: effects of chlordiazepoxide and mecamylamine. *J Pharmacol Exp Ther.* 1983; 224(2):334–340. [PubMed: 6822959]
- Gould, Robert W.; Czoty, Paul W.; Nader, Susan H.; Nader, Michael A. Effects of Varenicline on the Reinforcing and Discriminative Stimulus Effects of Cocaine in Rhesus Monkeys. *J Pharmacol Exp Ther.* 2011; 339(2):678–686.10.1124/jpet.111.185538 [PubMed: 21856860]
- Hennings, Esteban CP.; Kiss, Janos P.; De Oliveira, Karine; Toth, Peter T.; Vizi, E Sylvester. Nicotinic Acetylcholine Receptor Antagonistic Activity of Monoamine Uptake Blockers in Rat Hippocampal Slices. *J Neurochem.* 1999; 73(3):1043–1050.10.1046/j.1471-4159.1999.0731043.x [PubMed: 10461893]
- Mansbach RS, Rovetti CC, Freedland CS. The role of monoamine neurotransmitter systems in the nicotine discriminative stimulus. *Drug Alcohol Depend.* 1998; 52(2):125–134. S0376-8716(98)00085-4. [PubMed: 9800142]
- Matta SG, Balfour DJ, Benowitz NL, Boyd RT, Buccafusco JJ, Caggiula AR, Zirger JM. Guidelines on nicotine dose selection for in vivo research. *Psychopharmacology.* 2007; 190(3):269–319.10.1007/s00213-006-0441-0 [PubMed: 16896961]
- Mello NK, Newman JL. Discriminative and reinforcing stimulus effects of nicotine, cocaine, and cocaine + nicotine combinations in rhesus monkeys. *Exp Clin Psychopharmacol.* 2011; 19(3):203–214. 2011-07475-001. [PubMed: 21480727]
- Preston KL, Bigelow GE. Subjective and discriminative effects of drugs. *Behav Pharmacol.* 1991; 2(4 And 5):293–313. [PubMed: 11224073]
- Reid MS, Mickalian JD, Delucchi KL, Berger SP. A nicotine antagonist, mecamylamine, reduces cue-induced cocaine craving in cocaine-dependent subjects. *Neuropsychopharmacology.* 1999; 20(3): 297–307. S0893-133X(98)00076-1. [PubMed: 10063490]
- Schuster, CR.; Balster, RL. The discriminative stimulus properties of drugs. In: Thompson, T.; Dews, P., editors. *Advances in behavioral pharmacology.* Vol. 1. New York: Academic Press; 1977. p. 85-138.
- Spealman RD, Goldberg SR, Gardner ML. Behavioral effects of nicotine: schedule-controlled responding by squirrel monkeys. *J Pharmacol Exp Ther.* 1981; 216(3):484–491. [PubMed: 7205628]
- Stolerman IP, Garcha HS, Pratt JA, Kumar R. Role of training dose in discrimination of nicotine and related compounds by rats. *Psychopharmacology.* 1984; 84(3):413–419.10.1007/BF00555223 [PubMed: 6440189]
- Tsukada, Hideo; Nishiyama, Shingo; Ohba, Hiroyuki; Sato, Kengo; Harada, Norihiro; Kakiuchi, Takeharu. Cholinergic neuronal modulations affect striatal dopamine transporter activity: PET studies in the conscious monkey brain. *Synapse.* 2001; 42(3):193–195.10.1002/syn.10003 [PubMed: 11746716]
- Wise, Roy A. Dopamine and reward: The anhedonia hypothesis 30 years on. *Neurotox Res.* 2008; 14(2–3):169–183.10.1007/BF03033808 [PubMed: 19073424]
- Zachariou V, Caldarone BJ, Weathers-Lowin A, George TP, Elsworth JD, Roth RH, Picciotto MR. Nicotine receptor inactivation decreases sensitivity to cocaine. *Neuropsychopharmacology.* 2001; 24(5):576–589. S0893-133X(00)00224-4. [PubMed: 11282258]
- Zanetti L, Picciotto MR, Zoli M. Differential effects of nicotinic antagonists perfused into the nucleus accumbens or the ventral tegmental area on cocaine-induced dopamine release in the nucleus accumbens of mice. *Psychopharmacology.* 2007; 190(2):189–199.10.1007/s00213-006-0598-6 [PubMed: 17061109]

Figure 1.

Potency and time course of the discriminative stimulus effects of cocaine (0.1 – 1.0 mg/kg, IM; A) and nicotine (0.1 – 1.0 mg/kg, IM; B) in male rhesus monkeys trained to discriminate cocaine (0.32 mg/kg, IM) vs. saline ($n=5$). Top ordinates: percent cocaine-appropriate responding. Bottom ordinates: rates of responding in responses per second. Abscissae: time in min after injection. Symbols above “S” and “C” represent the group averages for all training sessions preceding test sessions when the saline- and cocaine-associated keys were correct, respectively. Filled symbols indicate statistical significance compared to saline ($p < 0.05$). Numbers in parentheses indicate the number of subjects contributing to that data point if < 5 subjects and indicative of a time point where a monkey failed to complete at least one ratio requirement during the response period.

Figure 2.

Cocaine-like discriminative stimulus effects of mecamylamine (0.32 – 1.8 mg/kg, IM) alone in rhesus monkeys ($n=5$). Mecamylamine was administered 15 min prior to a saline injection (time 0 min). Top ordinates: percent cocaine-appropriate responding. Bottom ordinates: rates of responding in responses per second. Abscissae: time in min. after injection administration. Symbols above “S” and “C” represent the group averages for all training sessions preceding test sessions when the saline- and cocaine- associated keys were correct, respectively. Filled symbols represent statistical significance compared to saline ($p < 0.05$). Numbers in parentheses indicate the number of subjects contributing to that data point if < 5 subjects and indicative of a time point where a monkey failed to complete at least one ratio requirement during the response period.

Figure 3.

Effects of mecamylamine (0.32 – 1.8 mg/kg, IM) pretreatment on the cocaine-like discriminative stimulus effects of cocaine (0.32 mg/kg; A) and nicotine (1.0 mg/kg; B). Mecamylamine was administered 15 min prior to cocaine or nicotine administration. Top ordinate: percent cocaine-appropriate responding. Bottom ordinate: rates of responding in responses per second. Abscissae: time in min. after cocaine or nicotine administration. Symbols above “S” and “C” represent the group averages for all training sessions preceding test sessions when the saline- and cocaine- associated keys were correct, respectively. Filled symbols represent statistical significance compared to saline ($p < 0.05$). Numbers in parentheses indicate the number of subjects contributing to that data point if < 5 subjects and indicative of a time point where a monkey failed to complete at least one ratio requirement during the response period.

Figure 4.

Effects of mecamylamine (1.8 mg/kg, IM) pretreatment on the cocaine-like discriminative stimulus effects of cocaine (A) and nicotine (B) in rhesus monkeys (N=3). Mecamylamine was administered 60 min prior to a cumulative dose test session for cocaine or nicotine. Top ordinate: percent cocaine-appropriate responding. Bottom ordinate: rates of responding in responses per second. Abscissae: cumulative cocaine or nicotine dose. Numbers in parentheses indicate the number of subjects contributing to that data point if < 3 subjects and indicative of a cumulative dose where a monkey failed to complete at least one ratio requirement during the response period.