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Effects of chronic binge-like ethanol consumption on cocaine self-administration in rhesus monkeys

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ABSTRACT

Background: Most cocaine abusers also abuse alcohol, but little is known about interactions that promote co-abuse. These experiments in rhesus monkeys determined the effects of >8 weeks of ethanol (EtOH) consumption on cocaine self-administration ($n = 6$), effects of dopamine (DA) receptor antagonists on cocaine reinforcement ($n = 3$–4 per drug) and the ability of the D2-like DA receptor agonist quinpirole to elicit yawning ($n = 3$).

Methods: Monkeys self-administered cocaine (0.0–1.0 mg/kg/injection, i.v.) under a 300-s fixed-interval schedule and the above-listed variables were measured before EtOH exposure. Next, monkeys consumed a sweetened, 4% EtOH solution in the home cage under binge-like conditions: 1 h, 5 days/week with daily intake equaling 2.0 g/kg EtOH. After approximately 8 weeks, measures were re-determined, then EtOH drinking was discontinued. Finally, acute effects of EtOH on cocaine self-administration were determined by infusing EtOH (0.0–1.0 g/kg. i.v.) prior to cocaine self-administration sessions ($n = 4$).

Results: In five of six monkeys, EtOH drinking increased self-administration of low cocaine doses but did not alter reinforcing effects of higher doses. Self-administration returned to baseline after EtOH access was terminated ($n = 3$). Effects of DA receptor antagonists on cocaine self-administration were not consistently altered after EtOH consumption, but the ability of quinpirole to induce yawning was enhanced in two of three monkeys. Acute EtOH infusions only decreased self-administration of lower cocaine doses.

Conclusions: Taken together, the data suggest that long-term EtOH exposure can increase sensitivity to cocaine, possibly by increasing D_3 receptor sensitivity. Data do not support a role for acute pharmacological interactions in promoting cocaine/EtOH co-abuse.

1. Introduction

Despite decades of research, cocaine abuse persists as a major public health problem and no pharmacotherapy has proven suitable for widespread clinical use (Kampman, 2010; Karila et al., 2011). The lack of success in translating preclinical hypotheses to effective medications indicates that significant barriers remain, but reasons for the disconnect between preclinical and clinical results are poorly understood. One clinical reality rarely incorporated into animal models is co-abuse of other substances. Humans who use or are dependent on multiple substances are typically excluded from clinical studies, and nearly all studies in laboratory animals limit exposure to a single drug of interest. This is understandable because characterizing the effects of two substances in combination is complex. In the case of alcohol and cocaine, however, such studies are critical. Estimates indicate that up to 90% of cocaine abusers also abuse alcohol (Grant and Harford, 1990; Helzer and Pryzbeck, 1988; Kampman et al., 2013; Tziortzis et al., 2011). Importantly, individuals who co-abuse alcohol commonly have more severe cocaine dependence, are more adversely affected by their drug use and are less likely to remain in treatment (Carroll et al., 1993; Heil et al., 2000; Higgins et al., 1994). Alarmingly, alcoholic cocaine users also report greater rates of unwanted sexual encounters and suicidal and homicidal behavior (Heil et al., 2000; Salloum et al., 1996).

The mechanistic basis for the pervasive co-abuse of alcohol and cocaine is incompletely understood, and studies characterizing the interactions between the drugs have produced mixed results. Enhancement of cocaine's abuse-related effects by EtOH would be expected based on its ability to increase striatal dopamine (DA) concentrations (e.g., Bradberry, 2002; Di Chiara and Imperato, 1988; Yoder et al., 2009). Moreover, similar alterations in brain DA systems – particularly D2 receptors – have been observed in alcoholics and cocaine abusers (e.g., Cosgrove, 2010; Volkow et al., 1996, 1999, 2002). When combined, cardiovascular effects

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of cocaine and EtOH can be enhanced, while effects on cognitive performance may be attenuated (Farre et al., 1993; Foltin and Fischman, 1988; Foltin et al., 1993; Higgins et al., 1992). Experiments in laboratory animals have also indicated that co-administration of cocaine and EtOH can produce more pronounced effects than either drug alone. These studies have primarily focused on motor endpoints such as locomotion and rates of lever pressing under schedules of reinforcement (Aston-Jones et al., 1984; Masur et al., 1989; Misra et al., 1989; Rech et al., 1978) rather than variables that more directly reflect cocaine's abuse-related effects. Only two studies have examined the effects of EtOH on cocaine self-administration in laboratory animals. In the first (Aspen and Winger, 1997), EtOH increased self-administration of cocaine and another DA uptake blocker, but not a mu opioid receptor agonist, in some monkeys. In the second (Winger et al., 2007), demand functions for cocaine/EtOH combinations were intermediate to those of either drug alone. In contrast, studies in humans demonstrate that alcohol can increase cocaine's reinforcing and pleasurable subjective effects (Farre et al., 1993; Higgins et al., 1996). Thus, although there is some evidence to suggest that EtOH can enhance some effects of cocaine, the data addressing this critical question are limited and involve only acute EtOH exposure. Due to limitations of studies with human drug abusers, including unknown extent of past and current drug use, unknown durations of abstinence, comorbid psychiatric disorders and inability to collect pre-drug "baseline" data, well-controlled, longitudinal experiments in animals are a critical step in understanding the causes and effects of polysubstance abuse.

The present studies were designed to assess two potential mechanisms by which long-term binge-like EtOH consumption may increase cocaine use. One possibility is that chronic exposure to EtOH results in enhancement of the reinforcing effects of cocaine. To address this possibility, dose–effect curves for cocaine self-administration were determined prior to EtOH exposure and again after monkeys had consumed EtOH 5 days per week for 8 weeks. Bottles containing a sweetened 4% EtOH solution were hung on monkeys' home cages for 1 h; monkeys could consume up to 2.0 g/kg per day. This regimen is consistent with the definition of "binge drinking" promulgated by the National Institute on Alcohol Abuse and Alcoholism: "a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08 g/dl. . .in about two hours;" http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking. Because the reinforcing effects of cocaine have been associated with DA D1-like and D2-like receptors, the sensitivity of cocaine self-administration to antagonists of these receptors was determined under both conditions. In addition, the ability of the D2-like DA receptor agonist quinpirole to elicit yawning was examined before and during the period of EtOH drinking. Although it interacts with all D2-like receptor subtypes, yawning elicited by quinpirole has been thoroughly characterized as an effect mediated by the D_3 receptor subtype of the D2-like family of DA receptors in rodents and monkeys (e.g., Collins et al., 2005, 2007; Martelle et al., 2007). Finally, after daily EtOH drinking was discontinued, the possibility that acute pharmacological interactions could increase cocaine reinforcement was tested by infusing EtOH intravenously just prior to self-administration sessions.

2. Materials and methods

2.1. Subjects

Eight adult male rhesus monkeys (*Macaca mulatta*) served as subjects. Each monkey was fitted with an aluminum collar (Primate Products, Redwood City, CA) and trained to sit calmly in a standard primate chair (Primate Products). Monkeys were housed individually in stainless steel cages in which water was available ad libitum. Monkeys were weighed weekly and fed enough food (Purina LabDiet Chow, St. Louis, MO), fresh fruit and vegetables daily to maintain healthy body weights without becoming obese as determined by daily inspection and periodic veterinary examinations. Body weights did not change significantly during these studies. Environmental enrichment was provided as outlined in the Institutional Animal Care and Use Committee's Non-Human Primate Environmental Enrichment Plan. Animal housing and handling and all experimental procedures were performed in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2011) and were approved by the Animal Care and Use Committee of Wake Forest University.

Each monkey was prepared with an indwelling venous catheter and subcutaneous vascular access port (VAP; Access Technologies, Skokie, IL) under sterile surgical conditions. An antibiotic (25 mg/kg kefzol, i.m.; Cefazolin sodium, Marsam Pharmaceuticals, Inc., Cherry Hill, NJ) was administered 1 h prior to surgery. Anesthesia was induced with ketamine (15 mg/kg, i.m.) and maintained with ketamine supplements. A catheter was inserted into a major vein (femoral or internal or external jugular) to the level of the vena cava. The distal end of the catheter was passed subcutaneously to a point slightly off the midline of the back, where an incision was made. The end of the catheter was attached to a VAP, which was placed in a subcutaneous pocket formed by blunt dissection.

Five to seven days per week, each monkey was seated in a primate chair and placed into a ventilated, sound-attenuating chamber ($0.76 \times 0.76 \times 1.5$ mm; Med Associates, St. Albans, VT). The back of the animal was cleaned with 3.15% chlorhexidine and 70% isopropyl alcohol (Prevantics Swab, PDI Inc, Orangeburg, NY) and the VAP was connected to an infusion pump (Cole-Parmer Instrument Co., Niles, IL) located outside the chamber via a 22-ga Huber Point Needle (Access Technologies) and tubing. The pump was operated for approximately 3 s to fill the port and catheter with the concentration of cocaine available for the session. A response key was located on one side of the chamber, above which was a horizontal row of three stimulus lights (green, red and white). A food receptacle was located below the key and was connected with a Tygon tube to a pellet dispenser (Med Associates) located on the top of the chamber for delivery of 1-g banana-flavored food pellets (Bio-Serv, Frenchtown, NJ). Experimental events occurring in these chambers were programmed and controlled by Med-PC software.

2.2. Cocaine self-administration

Monkeys were initially trained to respond on the key to receive a food pellet under a 300-s fixed interval schedule (FI 300). Initially, the green light was illuminated and every response produced a pellet and a 3-s illumination of the red light followed by a 10-s timeout (TO) period in which no lights were illuminated and responding had no scheduled consequences. Next, conditions were changed such that, after illumination of the green light, the first response after 1 s elapsed resulted in delivery of a food pellet (FI 1 s). If 30 s elapsed after the 1-s interval (a 30-s limited hold, LH, the green light was extinguished and a 10-s TO was initiated. Gradually, the FI and timeout durations were increased and the LH was decreased until all monkeys responded reliably on the terminal parameters: a FI 300-s schedule with a 10-s LH and 60-s TO. This schedule was presented 10 times each day, for a total session length of approximately 60 min. When monkeys responded reliably for 10 pellets each day, the reinforcer was changed to an infusion of 0.1 mg/kg cocaine (the maintenance dose). Dose–response curves were generated by substituting saline or single doses of cocaine (0.001–1.0 mg/kg/injection) for at least five days and until responding stabilized, defined as three consecutive days with ±1 infusions and no upward or downward trend. Cocaine self-administration sessions were conducted between 8 and 10 am 5–7 days per week.

2.3. Effects of dopamine receptor antagonists on cocaine self-administration

When self-administration of the maintenance dose of cocaine was stable, saline or a dose of a DA receptor antagonist was administered i.v. prior to the cocaine self-administration in subsets of a group of four monkeys (R-1606, R-1607, R-1757 and R-1758). Drugs tested (with doses and pretreatment times) were the D1-like receptor agonist SCH 23390 (0.01–0.3 mg/kg, 10 min, $n = 3$), the D2-like receptor antagonist eticlopride (0.001–0.01 mg/kg, 10 min, $n = 4$) and the D_3/D_4 receptor antagonist buspirone (0.03–1.0 mg/kg, 5 min, $n = 3$). Effects were re-determined during the period of daily EtOH consumption. Although testing of one drug was completed before another drug was tested, drugs were tested in mixed order across monkeys. In most cases, monkeys received saline and each dose that had effects (except those with clearly pronounced sedating and/or response rate-decreasing effects) at least twice in mixed order with test sessions occurring no more than twice per week.

2.4. Quinpirole-induced yawning

Yawning elicited by the DA D2-like receptor agonist quinpirole was measured in three monkeys (R-1607, R-1608, R-1758). While the monkey was seated in a primate chair in a quiet room, yawns were recorded with a video camera for 30 min (baseline). Next, at 30-min intervals, saline was administered i.v. followed by incremental doses of quinpirole (0.0032–0.3 mg/kg in ascending order) using cumulative dosing procedures (see Bergman and Spealman, 1988). Occurrences of yawning were recorded from the videos by two observers. A yawn was defined as full extension of the jaws, withdrawal of the lips and exposure of the teeth (Code and Tang, 1991).