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Effects of ethanol on cocaine self-administration in monkeys responding under a second-order schedule of reinforcement

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ABSTRACT

Background: Concurrent alcohol use among cocaine abusers is common but the behavioral variables that promote co-abuse are not well understood. The present study examined the effects of intragastric (i.g.) ethanol (EtOH) administration in monkeys responding under a schedule of cocaine reinforcement in which extensive drug seeking was maintained by conditioned stimuli.

Methods: Four adult male cynomolgus monkeys (*Macaca fascicularis*) were trained to respond under a second-order fixed-interval (FI) 600 s (fixed-ratio (FR) 30:S) schedule of cocaine (0.003–0.56 mg/kg/injection) presentation. Sessions ended after 5 injections or 90 min had elapsed. Different EtOH doses (0.5–2.0 g/kg, i.g.) were administered 30 min before the session, typically on Tuesdays and Fridays. Blood ethanol concentrations (BECs) were also assessed. Pattern of FI responding was assessed by determining quarter-life (QL) values.

Results: Cocaine self-administration was characterized as an inverted U-shaped function of dose; QL values increased monotonically with dose. EtOH pretreatments dose-dependently decreased self-administration at several cocaine doses in 3 of 4 monkeys. In one animal, EtOH increased low-dose cocaine-maintained responding. For all monkeys, QL values were increased by EtOH when low- and high-cocaine doses were self-administered, suggesting additive effects of EtOH and cocaine. Furthermore, BECs were not altered following cocaine self-administration.

Conclusions: The reductions in cocaine self-administration and the increases in QL values following EtOH, suggest that EtOH was enhancing cocaine-related conditioned reinforcement. A better understanding of the behavioral mechanisms that mediate the co-abuse of alcohol and cocaine will lead to improved treatments for both drugs.

1. Introduction

The ubiquity of poly-substance use among drug abusers is a well-documented characteristic that creates additional challenges related to psychosocial functioning and treatment outcome compared to patients abusing only one drug. Epidemiological evidence indicates that the majority of cocaine abusers report concurrent (past month) and simultaneous alcohol use (Grant and Harford, 1990; Helzer and Pryzbeck, 1988; Regier et al., 1990; SAMSHA, 2014; Tziortzis et al., 2011). In addition, 60–85 percent of treatment-seeking cocaine abusers also meet diagnostic criteria for lifetime alcohol dependence (Heil et al., 2001; Higgins et al., 1994; SAMSHA, 2014). Furthermore, clinical evidence indicates that alcohol consumption can induce relapse among cocaine abusers during abstinence (McKay et al., 1999) and treatment outcomes of patients with alcohol and cocaine co-dependence are often less successful than those of patients only dependent on cocaine (Anderson et al., 2009; Heil et al., 2001; Schmitz et al., 1997).

Despite the widespread prevalence of alcohol and cocaine co-abuse, the underlying behavioral mechanisms are not clear. In fact, preclinical studies using nonhuman primates have shown that ethanol (EtOH) either has no effect on cocaine self-administration (Czoty, 2015; Winger et al., 2007) or results in an increase in cocaine self-administration in only a subset of subjects (Aspen and Winger, 1997). In contrast, data from studies involving human subjects have shown that the combination of alcohol and cocaine produced more pleasurable subjective effects compared to either drug alone, as well as an increase in cocaine preference over alternative monetary reinforcers (Farré et al., 1997; Higgins et al., 1996).

A potentially important difference between these human and animal studies is the route of EtOH administration, which was oral in people but intravenous in monkeys. Pharmacokinetic stud-

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ies in humans demonstrate that orally administered EtOH prior to cocaine increases blood cocaine levels, decreases cocaine clearance, and produces the active metabolite cocaethylene (Farré et al., 1993, 1997; McCance-Katz et al., 1993, 1998; Perez-Reyes and Jeffcoat, 1992). Thus, the insensitivity of cocaine self-administration to EtOH pretreatment in previous preclinical studies may have been due to a dissimilar pharmacokinetic interaction between cocaine and intravenous alcohol. In order to provide a more translational assessment, the first aim of the present study was to examine the effects of intragastric (i.g.) administration of EtOH on cocaine self-administration. Surprisingly, the effects of i.g. EtOH on cocaine self-administration have not been examined in animals.

Another aim of the present study was to extend the findings of Czoty (2015), which examined the effects of EtOH on cocaine self-administration under a fixed-interval (FI) schedule to include the role of behavior maintained by conditioned stimuli in EtOH-induced changes in cocaine-maintained responding. To better understand how drugs affect FI responding, investigators can measure pattern of responding by calculating quarter-life (QL) values. QL indicates where within the FI the animal emitted 25% of its total responses. For example, QL values of 25% indicate a constant rate of responding throughout the interval and values above 25% indicate FI schedule-appropriate responding. Drugs that increase or decrease FI responding with an accompanying decrease in QL would indicate disruptions in schedule-appropriate responding. To examine behavior maintained by conditioned stimuli, monkeys were trained to self-administer cocaine under a second-order schedule of reinforcement. Responding maintained under these schedules can be used to examine the effects of drug pretreatments on self-administration that are less influenced by the reinforcer because extended sequences of behavior can be maintained by relatively few drug injections through presentations of a stimulus associated with the drug reinforcer (Kelleher, 1966). Behavior controlled under these conditions is analogous to the effectiveness of drugs in maintaining the long sequences of behaviors that are characteristic of human drug abusers involving the purchase, preparation and administration of the drug itself. Thus, examining the effects of EtOH on cocaine self-administration under a second-order schedule may lead to a better understanding of the environmental-pharmacological interactions that may promote co-abuse of alcohol and cocaine.

2. Material and methods

2.1. Subjects

Four adult male cynomolgus monkeys (*Macaca fascicularis*), with an extensive history of cocaine self-administration (~8 years) served as subjects. Monkeys were pair-housed in stainless-steel cages (76 × 60 × 70 cm), except during operant behavioral sessions and feeding, when the monkeys were housed individually. Each monkey was fitted with an aluminum collar (Model B008, Primate Products, Redwood City, CA) and trained to sit calmly in a primate restraint chair (Primate Products). All subjects were fed enough food (Purina LabDiet 5045, St Louis, MO) to maintain healthy body weights as determined by veterinary staff; body weights ranged from 5.3–6.3 kg (Table 1) and did not change significantly during this study. 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.

Table 1
Body weights and range of volume of ethanol delivered for each monkey.

Subject	Weight (kg)	Ethanol volume (ml)[a]
C-6525	5.3	13.3–53.0
C-7078	6.3	15.8–63.0
C-7084	5.7	14.3–57.0
C-7427	6.0	6.0–60.0

[a] The range was based on lowest and highest EtOH doses tested.

2.2. Surgery

Subjects were prepared with chronic indwelling venous catheters under aseptic conditions. Monkeys were initially anesthetized with ketamine (10 mg/kg, i.m.) and maintained with isoflurane throughout surgery. A catheter was inserted into a major vein (femoral, internal or external jugular) to the level of the posterior vena cava. The distal end of the catheter was passed subcutaneously to an incision made slightly off the midline of the back and attached to a subcutaneous vascular access port (Access Technologies, Skokie, IL). After surgery, an analgesic dose of ketoprofen (5.0 mg/kg, i.m.) was administered SID for three days.

2.3. Apparatus

Behavioral sessions were carried out in ventilated, sound-attenuating chambers (1.5 × 0.74 × 0.76 m; Med Associates, East Fairfield, VT) designed to accommodate a primate chair. An intelligence panel (48 × 69 cm) was located on the right side of the chamber that contained two photo-optic finger-poke apertures (Model 117–1007; Stewart Ergonomics, Inc., Furlong, PA) on each side with a horizontal row of three stimulus lights positioned 14 cm above each finger poke. For these studies, cocaine was available by responding on one of the two finger-pokes (switches) and the active switch was counterbalanced between monkeys. A food receptacle was located between the switches and connected with a Tygon tube to a pellet dispenser (Med Associates) located on the top of the chamber (food-reinforced responding was not examined in these monkeys). A peristaltic infusion pump (7531-10, Cole-Parmer Co., Chicago, IL) for delivering drug injections at a rate of approximately 1.5 ml/10 s was also located on the top of the chamber. White noise was continuously present in the room to mask extraneous noise.

2.4. Cocaine self-administration procedure

Monkeys were trained to self-administer cocaine under a second-order fixed-interval (FI) 600 s [fixed-ratio (FR) 30:S] schedule of i.v. drug injection. First, responding was maintained by 0.1 mg/kg cocaine under an FI 60 s schedule of reinforcement. Completion of the first response after 60 s resulted in extinction of the white light above the finger poke, illumination of a red light and delivery of cocaine over 10 s. The pairing of the red light with the cocaine injection was designed to make the red light a conditioned stimulus (CS). Over a 2–3 week period, the FI value was gradually increased to 600 s and the schedule changed to a second-order FI 600 s (FR 30:S), such that completion of every 30th response (FR 30) during the 600-s FI resulted in extinction of the white light and illumination of the red light for 2 s. Once the interval elapsed, the first FR 30 completed produced an intravenous injection of cocaine delivered over 10 s paired with the red light. A 60 s time out followed each injection, during which all lights were off and responses had no scheduled consequences. Daily sessions ended after the completion of five cycles of the second-order schedule or 90 min elapsed, whichever occurred first.

Once responding at the training dose of cocaine (0.1 mg/kg/injection) was deemed stable (overall response rates