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Pharmacology, Biochemistry and Behavior 74 (2003) 723–737
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Smoked heroin in rhesus monkeys: effects of heroin extinction and fluid availability on measures of heroin seeking

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Received 30 July 2002; received in revised form 18 November 2002; accepted 22 November 2002

Abstract

The purpose of the present study was to evaluate the reinforcing effects of smoked heroin in nonopioid-dependent nonhuman primates when an alternative reinforcer, sweetened fluid, was made available. Four adult male rhesus monkeys lived in three chambers, with heroin self-administration (0, 0.3, and 0.6 mg/kg) specific to one end of the chamber, oral sweetened fluid self-administration specific to the other end chamber, and no commodity available in the middle chamber. The length of time monkeys spent in the drug-associated chamber provided one measure of drug seeking (i.e., location preference). During self-administration sessions, a second-order schedule of reinforcement was used, with responding during the first component maintained by a brief presentation of the stimuli associated with reinforcement. Responding during the second component was maintained by a delivery of the reinforcer, and the associated stimuli. Responding during the first component provided a second measure of drug seeking. Monkeys also had choice trials each day, when they could choose to work for either commodity. Choice behavior provided a third measure of drug seeking. Each experimental day consisted of a smoking session (four smoking trials), a sweetened fluid session (four fluid trials), and a choice session (four choice trials). Monkeys typically completed all four smoking trials each day when either of the active heroin doses was available. They chose both heroin doses over fluid on 3.5 of the four choice trials, and they had a location preference for the heroin chamber. Under baseline conditions, the number of acquisition responses and the number of consumption responses (inhalations) were greater for the high dose of heroin compared to the low dose of heroin. Further, it took longer to extinguish the responding for the high dose of heroin compared to the low dose of heroin when a vehicle was substituted. During heroin extinction, acquisition responding for fluid increased, the number of fluid choices increased, and location preference shifted to the fluid chamber. These data suggest that in nondependent rhesus monkeys, measures of heroin seeking decreased when heroin was not available and seeking behavior shifted to the available alternative commodity.

Keywords: Second-order schedule; Location preference; Smoked heroin; Reinforcement; Rhesus monkey; Self-administration; Choice; Drug seeking

1. Introduction

Several drugs are abused by the smoked route of administration including nicotine, marijuana, cocaine, and heroin. Studies in humans have shown that the smoked route of cocaine (Evans et al., 1996) and heroin administration (Jenkins et al., 1994) produces similar pharmacologic and pharmacokinetic effects as the intravenous route for both of these drugs. The effectiveness of the smoked route, the relative ease and convenience of drug administration by the smoked route, and the perceived reduction in risk and infection via this route make the smoked route an attractive alternative for both initial users, as well as regular users. In fact, over the past decade, there has been a subtle shift from the intravenous route to other routes of heroin administration in some areas of the world (Hartgers et al., 1991; Griffiths et al., 1992; Barrio et al., 1998; Maher and Dixon, 1999; Swift et al., 1999). For example, in the Netherlands, 75–85% of all heroin users predominantly inhale heroin by "chasing the dragon" (Van Brussel and Buster, 1999).

Opioid abuse in humans often starts with occasional use (i.e., "chipping") such that these individuals are not physically dependent (Zinberg and Jacobson, 1976). However, limited heroin use often escalates to compulsive use, drug seeking, and physical dependence. Clearly, understanding

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0091-3057/02/$ – see front matter © 2002 Elsevier Science Inc. All rights reserved.
doi:10.1016/S0091-3057(02)01070-5

the transition from heroin use to compulsive heroin abuse and dependence, and the factors that can reduce heroin-seeking behavior and prevent this transition, are important for treatment. In spite of the use of the smoked route of heroin administration by humans, especially in some ethnic groups, only two published studies have examined the self-administration of smoked heroin by laboratory animals (Mattox and Carroll, 1996; Foltin and Evans, 2001a). In the study by Mattox and Carroll (1996), rhesus monkeys reliably smoked heroin (0.1–1.6 mg/kg) on 9–10 trials each day. In a previous study (Foltin and Evans, 2001a), the reinforcing effects of smoked heroin were examined in nonopioid-dependent rhesus monkeys using a procedure that combined aspects of both self-administration and conditioned place preference (CPP) procedures (Evans and Foltin, 1997; Foltin and Evans, 1997, 1999). In that study, four of six monkeys acquired heroin self-administration and reliably smoked heroin (0.3 and 0.6 mg/kg) on six to eight trials each day. Monkeys also developed a location preference for the chamber where heroin was self-administered. Under extinction conditions, heroin self-administration rapidly decreased.

The initial goals of this research are to focus on multiple measures of heroin seeking and taking under limited drug access conditions, and to provide a model of heroin use without dependence. To ensure that monkeys do not become physically dependent on heroin, the amount of drug intake is limited by restricting (1) the heroin doses available, (2) the number of doses that can be self-administered each day, and (3) the number of days each week that heroin is available. The purpose of the present study was to extend our initial study on smoked heroin (Foltin and Evans, 2001a), by providing nonopioid-dependent rhesus monkeys the ability to self-administer a nondrug alternative (sweetened fluid) in addition to smoked heroin to see if the presence of an alternative reinforcer would decrease heroin-seeking behavior. An effective environmental manipulation that decreases drug self-administration in laboratory animals is to have alternative reinforcers available (see review by Carroll, 1996), with numerous studies showing that drug self-administration can be modified by the presence of an alternative nondrug reinforcer such as food (Nader and Woolverton, 1991, 1992; Woolverton et al., 1997), as well as sweet substances (e.g., Carroll, 1987; Carroll et al., 1989, 1991; Comer et al., 1994; Rawleigh et al., 1996). In the present study, monkeys had the opportunity to self-administer heroin at certain times of the day and to self-administer sweetened fluid at different times of the day, followed by four discrete choice trials. Heroin choice is one measure of heroin seeking.

Responding for both reinforcers was maintained using a second-order schedule of reinforcement (see Goldberg et al., 1976; Markou et al., 1993; Arroyo et al., 1998). Responding during the first component results in the brief presentation of the stimuli that have been paired with the primary reinforcer and provides a measure of commodity acquisition or "drug seeking" before drug administration. Responding during the second component provides a measure of commodity consumption or "drug taking" such that completion of the schedule requirement results in the delivery of the reinforcer and the associated stimuli. Similarly, CPP procedures (e.g., Bardo et al., 1995; Schechter and Calcagnetti, 1993) provide a measure of drug seeking. Our location preference measure in monkeys is procedurally similar to the testing phase of CPP, although in our case the drug is self-administered and monkeys have the ability to move from chamber to chamber throughout the day. The length of time monkeys spend in the heroin-associated chamber provides a location preference estimate of drug seeking and of the conditioned reinforcing effects of the stimuli paired with the reinforcer, both in the presence (during experimental sessions) and in the absence of direct effects of the drug. This last measure of drug seeking has been shown to be sensitive to a variety of reinforcers and experimental manipulations (Foltin and Evans, 1997, 1999, 2001a; Evans and Foltin, 1997).

2. Method

2.1. Animals

Four adult male rhesus monkeys (*Macaca mulatta*), with previous exposure to smoked cocaine and smoked heroin and weighing between 7.6 and 10.1 kg, lived under the housing conditions described below for the 6-month duration of this experiment. Each monkey received a daily chow ration designed to maintain a stable body weight (6–12 high-protein monkey diet no. 5047 chow, 15 g/chow, 3.37 kcal/g, LabDiets; PMI Feeds, St. Louis, MO), chewable vitamins, and a piece of fruit daily. Body weights, determined weekly, remained stable throughout the study. All aspects of animal maintenance and experimental procedures complied with the US National Institutes of Health Guide for Care and Use of Laboratory Animals, and was approved by the New York State Psychiatric Institute Animal Care and Use Committee.

Each morning (Monday–Saturday), monkeys were assessed for the presence or absence of signs of opioid withdrawal symptoms (lying on the side or the abdomen, holding the abdomen, grimacing, retching, coughing, yawning, rigidity, dysphoric or unusual facial expressions, and "threatening outside of cage") by an observer blinded to drug (Aceto, 1984; Katz, 1986; Krystal and Redmond, 1983).

2.2. Apparatus

Each monkey had access to three identically sized chambers (61.5 cm wide×66.5 cm deep×88 cm high; Hazleton Systems, Aberdeen, MD) connected by 40×40 cm openings. For two of the monkeys, heroin self-administration occurred in the left-end chamber and fluid self-

administration occurred in the right-end chamber. These locations were reversed for the other two monkeys. No self-administered commodities were available in the middle chamber that separated the other two chambers. Water was freely available from spouts located on the back wall of all three chambers. To avoid biasing monkeys towards the heroin or sweetened fluid chamber, the daily food and fruit ration was provided in the center (neutral) chamber. An infrared heat and motion detector (Motion Sensor; Radio Shack, Fort Worth, TX) was mounted on each of the end chambers. When a monkey was in one of the end chambers, the detector for that chamber was activated. The location of each monkey was recorded every 30 s. All activities were monitored, and schedule contingencies were controlled by a customized software (Eureka Software, Cary, NC) running on two Macintosh (Cupertino, CA) 610 computers located in an adjacent area. The room lights were illuminated from 0700 to 1900 h.

Response panels were located on the front wall of all three chambers. Six session lights (CM 1820, 24 v; Chicago Miniature, Buffalo Grove, IL) with white lenses were evenly spaced around the outside edges of each panel. The smoked drug panel had one Lindsley lever (BRS-LVE, Beltsville, MD), with a light over it, mounted at the bottom; and a brass pipe mouthpiece, with two lights mounted above the pipe, and one light mounted to the monkey's right and slightly below the pipe. A pressure-activated relay (Micro Pneumatic Logic, Fort Lauderdale, FL) signaled the computer whenever a monkey sucked on the pipe. Due to limitations of the devices that provide vaporized drug on a heating coil (Hatsukami et al., 1990), a heated stem—more similar to that used by humans when smoking cocaine (Foltin et al., 1990)—was devised (Boni et al., 1991). A glass tube (10 mm) fitted with a screen for holding drug was set inside another glass tube (12 mm) mounted on the outside of the panel. The external pipe was wrapped by a heating coil (Cole-Parmer, Vernon Hills, IL), encased in fiberglass insulation (Cole Parmer), controlled with a heat controller (no. 515; George Ulanet, Newark, NJ). The heat source was maintained at a temperature of 280–300 °C. A brass stopper was fitted to the top of the stem arrangement in order to provide a sealed system, increasing the sensitivity of the pressure-sensitive switch. The inside glass stem and screens were changed daily. A pellet dispenser (model PDC-005; BRS-LVE, Beltsville, MD) was also mounted on the response panel. No pellets were delivered, but the sound of feeder activation was paired with drug delivery to provide an auditory cue. The fluid panel had two Lindsley levers, each with a light over it, mounted at the bottom; a spout for fluid delivery with a light over and beneath the spout; a peristaltic pump (7543-06 with pump head 7016; flow rate of 10 ml/min; Cole-Parmer, Chicago, IL); and a fluid source mounted on the outside. The center panel also had two Lindsley lever response manipulandums mounted at the bottom, but responses had no programmed consequences.

2.3. Operant conditioning schedule

Responding maintained by heroin or fluid was reinforced according to a second-order schedule of reinforcement: responding during the first component consisted of lever pulls, and responding during the second component consisted of puffs on the pipe for heroin or lever pulls on the consumption lever for fluid. The first component, indicated by a light over the acquisition lever, was a fixed interval (FI) 6-min schedule, with an embedded fixed ratio (FR) 20 second-order schedule [FI6′ (FR20: S)]. Thus, after every 20th response during the first component, the stimuli associated with heroin (two green flashing lights over the pipe) or fluid (two steady red lights above and below the spout) were presented for 10 s. Responding during this component provided a measure of heroin or fluid "seeking." The first FR20 completed after 6 min resulted in the acquisition lever light being extinguished and the light near the pipe (in the heroin chamber) or the light over the consumption lever (in the fluid chamber) being illuminated, indicating the availability of reinforcement according to the second component of the schedule. The second component, lasting 2 min, was an FR5 schedule with a 10-s time out after reinforcer delivery, when responding had no programmed consequences [FR5 (to 10″)]. In the heroin chamber, the completion of the first FR (sucks on the pipe) during the second component resulted in the delivery of heroin, two green flashing lights over the pipe, and the sound of the "click" of the pellet dispenser. This component provided a measure of heroin "taking." Subsequent sucks on the pipe during the second component resulted only in the sound of the "click" of the pellet dispenser and the flashing lights. This procedure was used to reinforce multiple sucks on the heroin delivery system to ensure that the monkeys inhaled most, or all, of the smoked heroin. Heroin powder (0, 0.3, and 0.6 mg/kg 3,6-diacetyl-morphine HCl; courtesy of the National Institute on Drug Abuse) was dissolved in 95% ethanol to a concentration of 60 mg/ml. The liquid heroin (or vehicle) was delivered by human hand via syringe into the stem system. Larger doses were not tested to prevent opioid dependence.

Similarly, in the fluid chamber, completion of the first FR during the second component (pulls on the consumption lever) resulted in the delivery of 12 ml of fluid (four 15-s deliveries with a 5-s pause between deliveries) and the two steady red lights above and below the spout. Subsequent responses during the second component only resulted in the steady red lights. The fluid consisted of a 0.25-kcal/ml dilute strawberry–raspberry-flavored solution [260 g of glucose (3.85 kcal/g; Sigma, St. Louis, MO) dissolved in 4000 ml of tap water with one packet of Increditberry Kool-Aid (Kraft General Foods, White Plains, NY)].

All monkeys had been previously trained to smoke heroin, delivered as heroin powder, under the same operant schedule (Foltin and Evans, 2001a) and had experience self-administering sweetened fluid under a similar operant

schedule (Evans and Foltin, 1997). Table 1 describes an experimental day that started at 0800 h with a 30-min neutral session. During a neutral session, session lights were illuminated in the center chamber, but responding had no programmed consequences. The neutral session lights served to activate the heater controller to maintain the heat in the stem of the drug panel. From 0830 to 0930 h, animals had a 1-h heroin smoking session that consisted of four smoking trials, each separated by a 9-min neutral session. Thus, smoked heroin was available with an interdose interval of 15 min (i.e., the duration of the neutral session between heroin trials plus the duration of the heroin-seeking component was 15 min). The heroin smoking session was followed by a 1-h neutral session, and then a 1-h fluid session occurred from 1030 to 1130 h. The fluid session also consisted of four fluid trials, each separated by a 9-min neutral session to maintain the 15-min interreinforcer interval. Then a 1-h neutral session separated the fluid session from the choice session that occurred from 1230 to 1330 h. The choice session consisted of four choice trials, each separated by a 9-min neutral session. During choice sessions, session lights and acquisition lever lights in both the heroin and fluid chambers were illuminated. The first response on either acquisition lever terminated the schedule opportunity in the alternate chamber and initiated the acquisition component for the chosen commodity. After the 1-h choice session, a 4.5-h no-commodity session (no stimuli illuminated in any of the chambers) occurred. Thus, location preference data were collected throughout the day from 0800 to 1800 h. The maximum number of heroin doses a monkey could receive each day was eight. The daily chow allotment was divided into three meals provided 1 h before each session of the day (i.e., 0730, 0930, and 1130 h). Experimental sessions occurred from Monday through Friday.

Table 1
Daily schedule of events (Monday–Friday)

Time (h)	Event	
0730	Feed 1/3 food ration	
0800–0830	Neutral session[a]	
0830–0930	Heroin smoking session	
	0830–0845	Trial 1
	0845–0900	Trial 2
	0900–0915	Trial 3
	0915–0930	Trial 4
0930	Feed 1/3 food ration	
0930–1030	Neutral session	
1030–1130	Sweetened fluid session	
	1030–1045	Trial 1
	1045–1100	Trial 2
	1100–1115	Trial 3
	1115–1130	Trial 4
1130	Feed 1/3 food ration	
1130–1230	Neutral session	
1230–1330	Choice session: heroin vs. fluid	
	1230–1245	Choice 1
	1245–1300	Choice 2
	1300–1315	Choice 3
	1315–1330	Choice 4
1330–1800	No-commodity session[b]	

[a] Neutral session: During a neutral session, session lights were illuminated in the center chamber. The neutral session lights served to activate the heater controller to maintain the heat in the stem of the drug panel.

[b] No-commodity session: During the no-commodity session, no stimuli were illuminated in any of the chambers, but the location detectors continued to monitor where the animals were. Thus, location preference data were collected throughout the day from 0800 to 1800 h.

2.4. Procedure

Table 2 describes the four extinction testing conditions and the order of testing in each monkey. Responding of two monkeys was initially reinforced with 0.3 mg/kg heroin, while responding of the other two monkeys was initially reinforced with 0.6 mg/kg heroin. Once responding and location preference were stable (i.e., no increasing or decreasing trends based on the number of acquisition and consumption responses, the total number of heroin and fluid deliveries, and time spent in the heroin chamber for each monkey) for a minimum of four successive experimental days, the effects of heroin and fluid extinction under the initial heroin dose condition were determined. The experimental sessions continued as before with all of the stimuli associated with heroin or sweetened fluid delivery being presented, but during extinction testing, the vehicle (95% ethanol for heroin or water for sweetened fluid) was substituted. However, all of the stimuli associated with heroin or sweetened fluid delivery were presented. When responding had decreased to less than 30% of baseline, or after a minimum of 4 days, heroin or sweetened fluid was reinstated. When responding was stable again, the effects of extinction of the other commodity were tested. Then monkeys were switched to the other heroin dose (e.g., the two monkeys that had been tested with the low dose began receiving the high dose) and once responding at the new dose had stabilized, extinction testing of heroin and sweetened fluid was conducted. Thus, all monkeys were exposed to extinction of heroin and sweetened fluid when the low dose of heroin was available for self-administration and when the high dose of heroin was available for self-administration, with the order of heroin dose condition and the order of heroin and sweetened fluid extinction counterbalanced across the four monkeys.

Urine toxicology was accomplished once when stable responding was maintained with 0.3 mg/kg heroin and once when stable responding was maintained with 0.6 mg/kg heroin. Urine was collected from sheet pans placed beneath the heroin chamber at 0830 h (before the experimental day), 1030 h (after the first four smoking trials), and 1230 h on a day when monkeys were confined to the heroin chamber. Urinary heroin, metabolite levels, primarily morphine, were determined using semiquantitative urinalysis (Abbott TDX, Chicago, IL).

Table 2
Design and order of conditions

Condition	Event	
Condition A	Baseline[a]	0.6 mg/kg smoked heroin and fluid available
High-dose heroin	Extinction[b]	Vehicle substituted for heroin
Heroin extinction	Recovery[c]	0.6 mg/kg smoked heroin and fluid available
Condition B	Baseline	0.3 mg/kg smoked heroin and fluid available
Low-dose heroin	Extinction	Vehicle substituted for heroin
Heroin extinction	Recovery	0.3 mg/kg smoked heroin and fluid available
Condition C	Baseline	0.6 mg/kg smoked heroin and fluid available
High-dose heroin	Extinction	Water substituted for sweetened fluid
Fluid extinction	Recovery	0.6 mg/kg smoked heroin and fluid available
Condition D	Baseline	0.3 mg/kg smoked heroin and fluid available
Low-dose heroin	Extinction	Water substituted for sweetened fluid
Fluid extinction	Recovery	0.3 mg/kg smoked heroin and fluid available

Animal	Order of conditions tested			
	First	Second	Third	Fourth
CIA	A	C	D	B
89D	B	D	C	A
COX	D	B	A	C
CV6	C	A	B	D

[a] Baseline: Stable responding for a minimum of 4 days before extinction testing.

[b] Extinction: This condition lasted for a minimum of 4 days or until responding decreased to less than 30% of baseline responding.

[c] Recovery: This condition typically consisted of the first 4 days of commodity reinstatement. However, in some cases, responding on the first day of commodity reinstatement was still low following extinction and Days 2–5 were used for Recovery.

2.5. Data analysis

The number of reinforcers delivered, the number of responses, the latency to the first response, the overall response rate during acquisition, and the consumption components were summarized for heroin and fluid sessions. The number of heroin and fluid choices made during choice sessions each day was also summarized. For all analyses, the four experimental days immediately before extinction (Baseline), the last 4 days of extinction testing (Extinction), and the first four stable days following commodity reinstatement (Recovery) across the four monkeys were used for each of the four extinction tests: (1) high-dose heroin available, heroin extinction; (2) low-dose heroin available, heroin extinction; (3) high-dose heroin available, fluid extinction; and (4) low-dose heroin available, fluid extinction. Recovery consisted of the first four stable days after commodity reinstatement. In the majority of cases, responding rapidly returned within the first or second day of commodity reinstatement. Therefore, Days 1–4 or Days 2–5 after reinstatement were typically used for Recovery. For each extinction test, the various measures were analyzed separately using two-factor, repeated-measures analyses of variance (ANOVA) with Condition (Baseline, Extinction, Recovery) as the first factor, and Day (4 days) as the second factor. Three planned comparisons were conducted on the Condition factor (Baseline vs. Extinction; Extinction vs. Recovery; Baseline vs. Recovery).

Using the three-chamber living arrangement, rhesus monkeys spent much time walking (or running) among all three chambers, and often sat on the squeeze bar at the side of the chambers with their tails in one chamber and their heads in another. The location system categorized monkeys as being in the middle no-commodity chamber if they were moving amongst chambers, or if they were perched partly in the middle chamber and partly in another commodity chamber. Finally, if a monkey was asleep or "lost" to the location detector, he was classified as being in the middle chamber. Thus, time spent in the heroin and fluid chambers was estimated conservatively, and the middle chamber was the default location. The length of time that monkeys spent in each chamber was summarized for three stimulus conditions: (1) daily total during the 10-h session, (2) heroin or heroin-choice sessions (heroin stimuli illuminated and heroin available), and (3) fluid or fluid-choice sessions (fluid stimuli illuminated and fluid available). For each extinction test, the various measures were analyzed separately using three-factor, repeated-measures ANOVA with Chamber (Heroin, Fluid) as the first factor, Condition (Baseline, Extinction, Recovery) as the second factor, and Day (4 days) as the third factor. Three planned comparisons were conducted comparing the time spent in the heroin and fluid chamber as a function of Condition (Baseline, Extinction, Recovery).

3. Results

3.1. Opioid dependence, urinary opioid levels, and extinction

Based on the morning assessments, no monkey was ever observed to have any opioid withdrawal symptoms, suggesting that the doses used and limited access adequately prevented the development of opioid dependence. Further,

there was no evidence of opioid withdrawal symptoms and no change in food intake on weekends when no sessions were conducted or during periods of heroin extinction. However, during heroin smoking sessions, all monkeys showed signs of intoxication. This was most commonly expressed as excessive scratching, but monkeys were also observed to occasionally appear to be asleep (e.g., ''nodding'') during trials.

In the morning (0830 h) before the heroin session, all monkeys had morphine-positive urine levels (849±587 ng/ml for 0.3 mg/kg heroin and 443±156 ng/ml for 0.6 mg/kg heroin), indicating residual heroin from the previous day. After the morning session (0830–0930 h), urine morphine levels collected at 1030 h were increased for both doses of heroin relative to the 0830-h sample, although there was no consistent evidence of a dose-related increase (3378±3013 ng/ml for 0.3 mg/kg heroin and 1486±664 ng/ml for 0.6 mg/kg heroin), due primarily to one animal who had extremely high opioid levels after the 0.3 mg/kg heroin session. Three hours after the morning session, urinary morphine levels were 2097±1389 ng/ml for 0.3 mg/kg heroin and 1766±1015 ng/ml for 0.6 mg/kg heroin. Thus, all four monkeys had measurable urinary opioid levels indicating that they were inhaling the heroin.

When the high dose of heroin was replaced with the vehicle (95% ethanol), responding decreased substantially (i.e., 25–30% of baseline) in 11.5 days (range: 6–16 days). In contrast, when the low dose of heroin was replaced with vehicle, responding decreased substantially in 7.5 days (range: 6–9 days). It took significantly more days to extinction when the high dose of heroin was available compared to the low dose of heroin ($P<.036$), and this difference was not related to an order effect since all conditions were counterbalanced across animals. When sweetened fluid was replaced with water, responding decreased substantially in approximately 5 days (range: 4–6 days), regardless of the heroin dose that was available. When the high dose of heroin was available (combined across heroin and fluid extinction conditions), the number of acquisition responses tended to be greater during high-dose heroin sessions than during fluid sessions (382 vs. 241 responses; $P=.09$) at baseline. However, when the low dose of heroin was available, the number of heroin and fluid acquisition responses was similar (299 vs. 292 responses). In addition, the number of acquisition responses during heroin sessions tended to be greater when the high dose of heroin was available than when the low dose of heroin was available (382 vs. 299 responses; $P=.09$).

3.2. Heroin extinction

3.2.1. High dose heroin (0.6 mg/kg) extinction when fluid was available

Fig. 1 (top panels) shows that under baseline conditions, monkeys typically completed all four acquisition (''seeking'') and consumption (''taking'') components during heroin sessions, whereas they completed approximately 2.4 components during fluid sessions. During heroin extinction, the number of acquisition [$F(1,2)=98.0$, $P<.0001$] and consumption [$F(1,2)=157.5$, $P<.0001$] components completed during heroin sessions significantly decreased compared to baseline. Correspondingly, there was a small but nonsignificant increase in the number of fluid acquisition and consumption components completed during fluid sessions, even though these sessions occurred after heroin sessions. When 0.6 mg/kg heroin was reinstated (Recovery), the number of acquisition and consumption components completed during both heroin and fluid sessions returned to baseline levels.

Fig. 1 (center panels) shows the mean number of acquisition responses (i.e., one measure of seeking) and consumption responses (taking) during heroin and fluid sessions. Animals emitted an average of 373 acquisition responses during heroin sessions and an average of 247 acquisition responses during fluid sessions under baseline conditions. During heroin extinction, the number of heroin acquisition responses significantly decreased [$F(1,2)=66.5$, $P<.0002$], with a corresponding increase [$F(1,2)=6.7$, $P<.05$] in the number of fluid acquisition responses during fluid sessions. During the consumption component, animals sucked the pipe an average of 117 times during heroin sessions at baseline even though the FR requirement was five, with only 20 sucks required across the four heroin trials. This demonstrates that monkeys continued to suck and inhale the heroin. During heroin extinction, the number of sucks on the pipe significantly decreased [$F(1,2)=50.7$, $P<.0004$], but when 0.6 mg/kg heroin was reinstated, responding during both heroin and fluid sessions returned to baseline levels. Overall, there were few changes in latency or response rate (data not shown), with one exception: during heroin extinction, latency to the first response [$F(1,2)=26.4$, $P<.003$] was significantly increased during the consumption components of heroin sessions.

The lower panels of Fig. 1 show choice and location preference—the other two measures of heroin seeking. Heroin was chosen over fluid on three of the four choice trials under baseline conditions. During heroin extinction, there was a significant decrease in heroin choice [$F(1,2)=24.4$, $P<.003$], with a corresponding increase in fluid choice [$F(1,2)=17.2$, $P<.006$]. When 0.6 mg/kg heroin was reinstated, the choice of heroin over fluid returned to baseline levels. Similarly, under baseline conditions, monkeys spent significantly [$F(1,2)=11.5$, $P<.02$] more time in the heroin chamber (138 min) than in the fluid chamber (55 min) throughout the day when the high dose of heroin was available. During heroin extinction, the length of time spent in the heroin chamber decreased while the length of time spent in the fluid chamber increased, such that similar lengths of time were spent in the two chambers. The location preference for the heroin chamber did not fully recover to baseline levels after 0.6 mg/kg heroin was

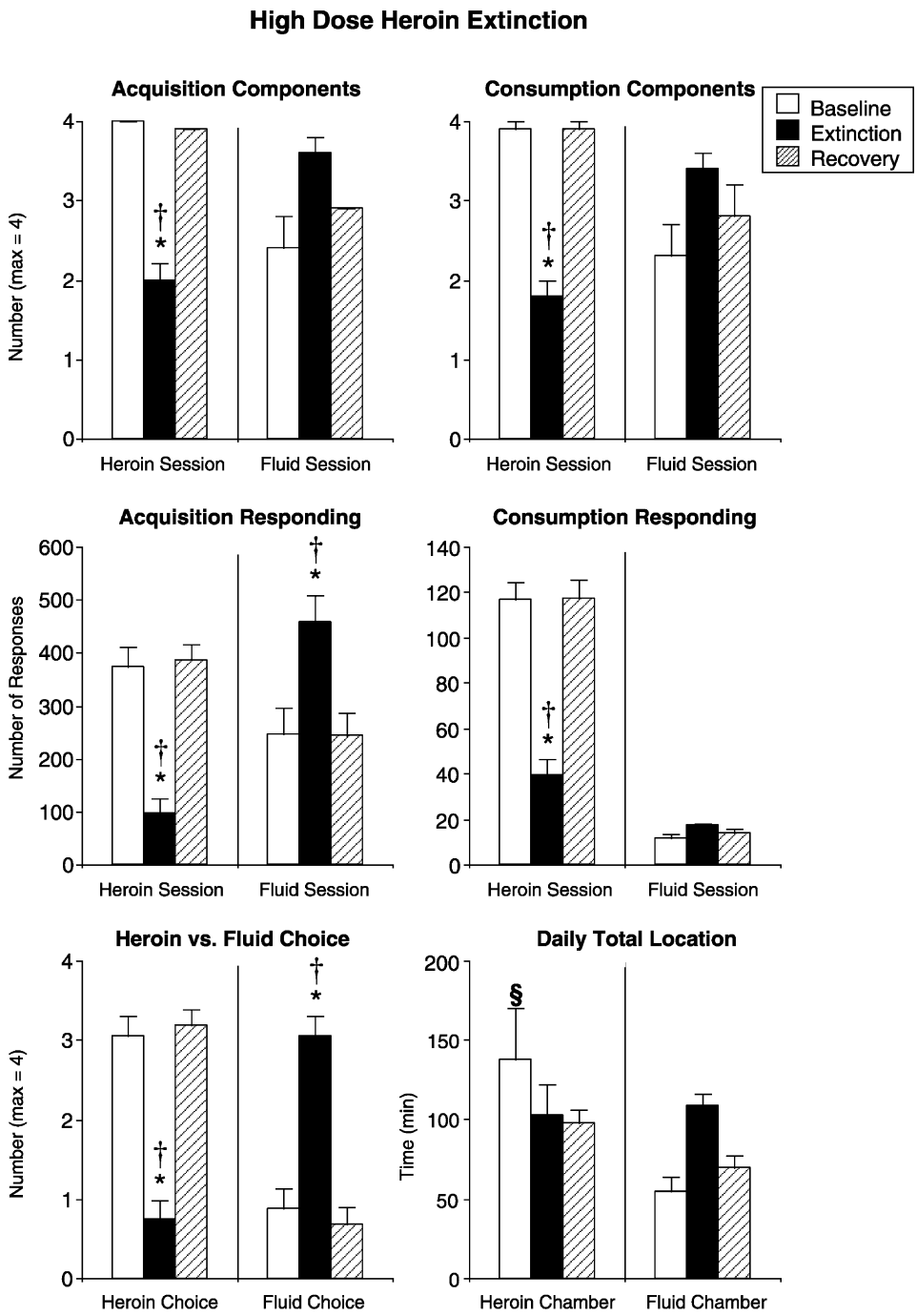

Fig. 1. Responding during heroin and fluid sessions, and choice and location preference as a function of high-dose (0.6 mg/kg) heroin extinction. Open bars represent baseline (the mean of the 4 days immediately before extinction testing); solid bars represent extinction (the mean of last 4 days of extinction testing); and hatched bars represent recovery (the mean of the first 4 days after the reinforcer was reinstated). Each bar represents the average across the four monkeys in each condition and error bars represent 1 S.E.M. The top panels show the number of acquisition and consumption components completed during heroin and fluid sessions (maximum of four heroin trials and four fluid trials each day). The center panels show the total number of acquisition and consumption responses made during heroin and fluid sessions. Responding during the acquisition components was reinforced using a FI 6-min schedule, with an embedded FR20 second-order schedule [FI6′ (FR5: S)] by the presentation of the stimulus lights that were paired with heroin smoking (green flashing lights) or oral fluid (red steady lights). Responding during the consumption component, lasting 2 min, was reinforced using an FR5 schedule. This involved sucks on the pipe for heroin or lever pulls for fluid. Completion of the first FR resulted in the delivery of heroin or fluid and the stimuli paired with that reinforcer. Subsequent completed FRs during the second component only resulted in the stimuli paired with the reinforcer. The bottom left panel shows the number of heroin and fluid choices (maximum of four choice trials each day). The bottom right panel shows the mean length of time that monkeys spent in the heroin and the fluid chamber throughout the day. *Indicates a significant ($P<.05$) difference between Baseline and Extinction. †Indicates a significant difference between Extinction and Recovery. $^{\Delta}$Indicates a significant difference between Baseline and Recovery. §Indicates a significant difference in location preference between the heroin chamber and the fluid chamber.

reinstated. A similar pattern of location preference was observed during heroin sessions and fluid sessions, with the exception that in both cases, location preference for the appropriate commodity returned to baseline levels when heroin was reinstated (data not shown).

3.2.2. Low-dose heroin (0.3 mg/kg) extinction when fluid was available

The effects of low-dose (0.3 mg/kg) heroin extinction were similar to what was shown above for high-dose heroin extinction. Fig. 2 shows that under baseline conditions, monkeys typically completed all four acquisition and consumption components during heroin sessions, whereas they completed approximately 2.7 components during fluid sessions. During heroin extinction, the number of acquisition [$F(1,2)=80.5$, $P<.0001$] and consumption [$F(1,2)=253.6$, $P<.0001$] components completed during heroin sessions significantly decreased compared to baseline. Correspondingly, during heroin extinction, there was a small increase (nonsignificant) in the number of fluid acquisition and consumption components completed during fluid sessions. When 0.3 mg/kg heroin was reinstated, the number of acquisition and consumption components completed during both heroin and fluid sessions returned to baseline levels.

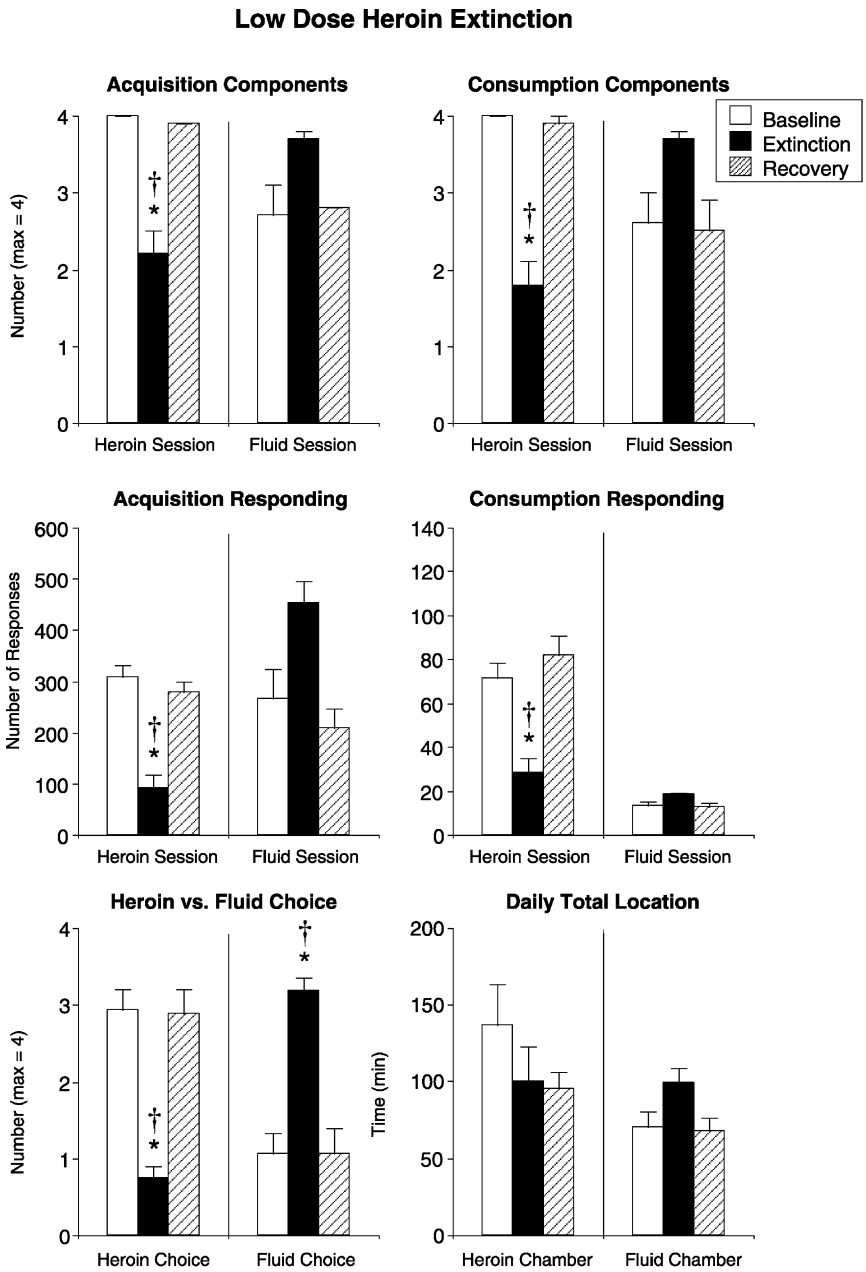

Fig. 2. Responding during heroin and fluid sessions, and choice and location preference as a function of low-dose (0.3 mg/kg) heroin extinction (see Fig. 1 for details).

Fig. 2 (center panels) also shows that animals emitted an average of 309 acquisition responses during heroin sessions and an average of 267 acquisition responses during fluid sessions. During heroin extinction, the number of heroin acquisition responses significantly decreased [$F(1,2)=55.4$, $P<.0003$], with a small but nonsignificant increase in the number of fluid acquisition responses during fluid sessions. During the consumption component, animals sucked the pipe an average of 71 times during heroin sessions and the number of sucks on the pipe significantly decreased [$F(1,2)=18.9$, $P<.005$] during heroin extinction. When 0.3 mg/kg heroin was reinstated, responding during both heroin and fluid sessions returned to baseline levels. There were few changes in latency or response rate, although during heroin extinction, latency to the first response increased during both the acquisition [$F(1,2)=12.4$, $P<.02$] and consumption components of heroin sessions [$F(1,2)=7.5$, $P<.04$].

The lower panels of Fig. 2 show that heroin was chosen over fluid on three of the four choice trials under baseline conditions. During heroin extinction, there was a significant decrease in heroin choice [$F(1,2)=16.8$, $P<.007$], with a corresponding increase in fluid choice [$F(1,2)=12.9$, $P<.02$]. When 0.3 mg/kg heroin was reinstated, the choice of heroin over fluid returned to baseline levels. With respect to location preference, under baseline conditions, monkeys tended to spend more time ($P<.07$) in the heroin chamber (137 min) than in the fluid chamber (70 min) throughout the day. During heroin extinction, there was a slight decrease in the overall length of time spent in the heroin chamber and a slight increase in the length of time spent in the fluid chamber, and these location preferences did not change when 0.3 mg/kg heroin was reinstated. Similarly, during heroin sessions, location preference for the heroin chamber decreased during heroin extinction relative to baseline, with a corresponding increase in time spent in the fluid chamber during fluid sessions, and these location preferences returned to baseline levels when 0.3 mg/kg heroin was reinstated (data not shown).

3.3. Fluid extinction

3.3.1. Fluid extinction when high-dose heroin (0.6 mg/kg) was available

Fig. 3 (top panels) shows that under baseline conditions, monkeys typically completed all four acquisition and consumption components during heroin sessions, whereas they completed approximately three components during fluid sessions. During fluid extinction, the number of acquisition [$F(1,2)=15.3$, $P<.008$] and consumption [$F(1,2)=20.1$, $P<.005$] components completed during fluid sessions significantly decreased compared to baseline. When fluid was reinstated, the number of acquisition components completed during fluid sessions tended to be lower than baseline levels and the number of consumption components completed during fluid sessions did not fully recover to baseline levels [$F(1,2)=8.4$, $P<.03$]. However, there was no change in the number of acquisition and consumption components completed during heroin sessions as a function of fluid extinction or fluid reinstatement.

Fig. 3 (center panels) shows that animals emitted an average of 392 acquisition responses during heroin sessions and an average of 235 acquisition responses during fluid sessions under baseline conditions. During fluid extinction, the number of fluid acquisition responses [$F(1,2)=10.1$, $P<.02$] and the number of consumption responses [$F(1,2)=20.2$, $P<.004$] significantly decreased. When fluid was reinstated, the number of acquisition and consumption responses during fluid sessions was still decreased relative to baseline. Instead, there was a small increase [$F(1,2)=9.0$, $P<.03$] in the number of heroin consumption responses during heroin sessions when fluid was reinstated. Overall, there were few changes in latency or response rate. During fluid extinction, latency to the first response during the consumption components of fluid sessions significantly increased [$F(1,2)=8.7$, $P<.03$] and, correspondingly, latency to the first response during the consumption components of heroin sessions significantly decreased [$F(1,2)=10.5$, $P<.04$] (data not shown).

The lower panels of Fig. 3 show that heroin was chosen over fluid on approximately 3.4 of the four choice trials under baseline conditions and this choice pattern did not vary as a function of fluid extinction or fluid reinstatement. With respect to location preference, under baseline conditions monkeys spent significantly [$F(1,2)=40.4$, $P<.0007$] more time in the heroin chamber (104 min) than in the fluid chamber (60 min) throughout the day and this location preference for the heroin chamber did not vary during fluid extinction or when fluid was reinstated. Similarly, during both heroin and fluid sessions, monkeys spent significantly more time in the heroin chamber compared to the fluid chamber regardless of the condition (data not shown).

3.3.2. Fluid extinction when low-dose heroin (0.3 mg/kg) was available

Fig. 4 (top panels) shows that under baseline conditions, monkeys typically completed all four acquisition and consumption components during heroin sessions, whereas they completed approximately 3.4 components during fluid sessions. During fluid extinction, the number of acquisition [$F(1,2)=16.3$, $P<.007$] and consumption [$F(1,2)=28.1$, $P<.002$] components completed during fluid sessions significantly decreased compared to baseline, and recovered to baseline levels. There was no change in the number of acquisition and consumption components completed during heroin sessions as a function of fluid extinction or fluid reinstatement.

Fig. 4 (center panels) shows that animals emitted an average of 290 acquisition responses during heroin sessions and an average of 318 acquisition responses during fluid sessions. During fluid extinction, the number of fluid acquisition responses significantly decreased [$F(1,2)=17.2$, $P<.006$], as did the number of heroin acquisition responses

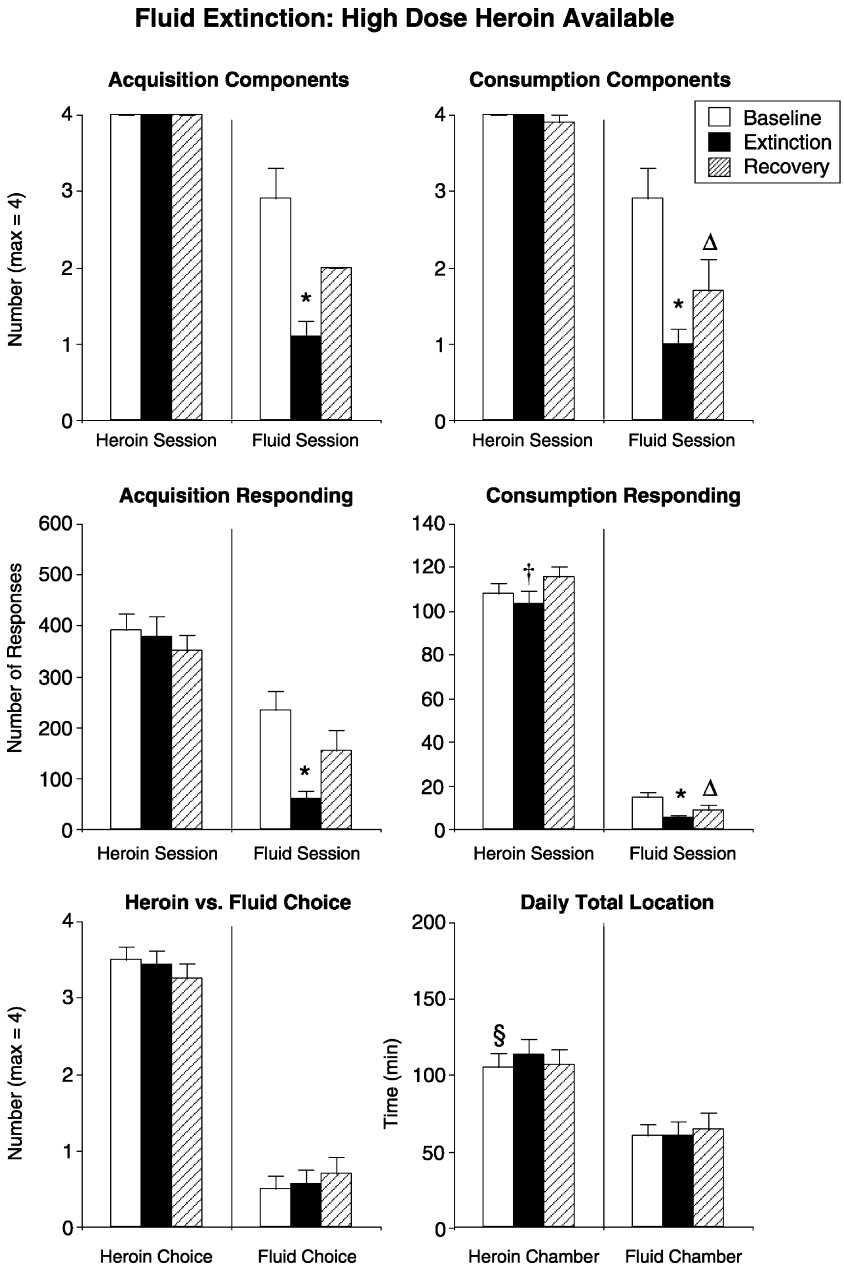

Fig. 3. Responding during heroin and fluid sessions, and choice and location preference as a function of fluid extinction when the high-dose (0.6 mg/kg) heroin was available (see Fig. 1 for details).

during heroin sessions [$F(1,2)=8.9$, $P<.03$]. Similarly, the number of consumption responses during fluid sessions significantly decreased during fluid extinction [$F(1,2)=22.2$, $P<.004$], with no change in the number of responses during heroin sessions. When fluid was reinstated, responding during fluid and heroin sessions returned to baseline levels. Further, there were several changes in latency and response rate. During fluid extinction, latency to the first response during the acquisition [$F(1,2)=5.6$, $P<.06$] and consumption components [$F(1,2)=21.8$, $P<.01$] of fluid sessions increased and the response rate during consumption components of fluid sessions decreased [$F(1,2)=14.5$, $P<.009$].

The lower panels of Fig. 4 show that when 0.3 mg/kg heroin was available, heroin was chosen over fluid on approximately three of the four choice trials under baseline conditions. During fluid extinction, heroin choice tended to increase ($P<.06$) with a corresponding decrease in fluid choice ($P<.06$), but the choice pattern returned to baseline levels when fluid was reinstated. With respect to location preference, under baseline conditions monkeys spent a similar length of time in the heroin (101 min) and fluid

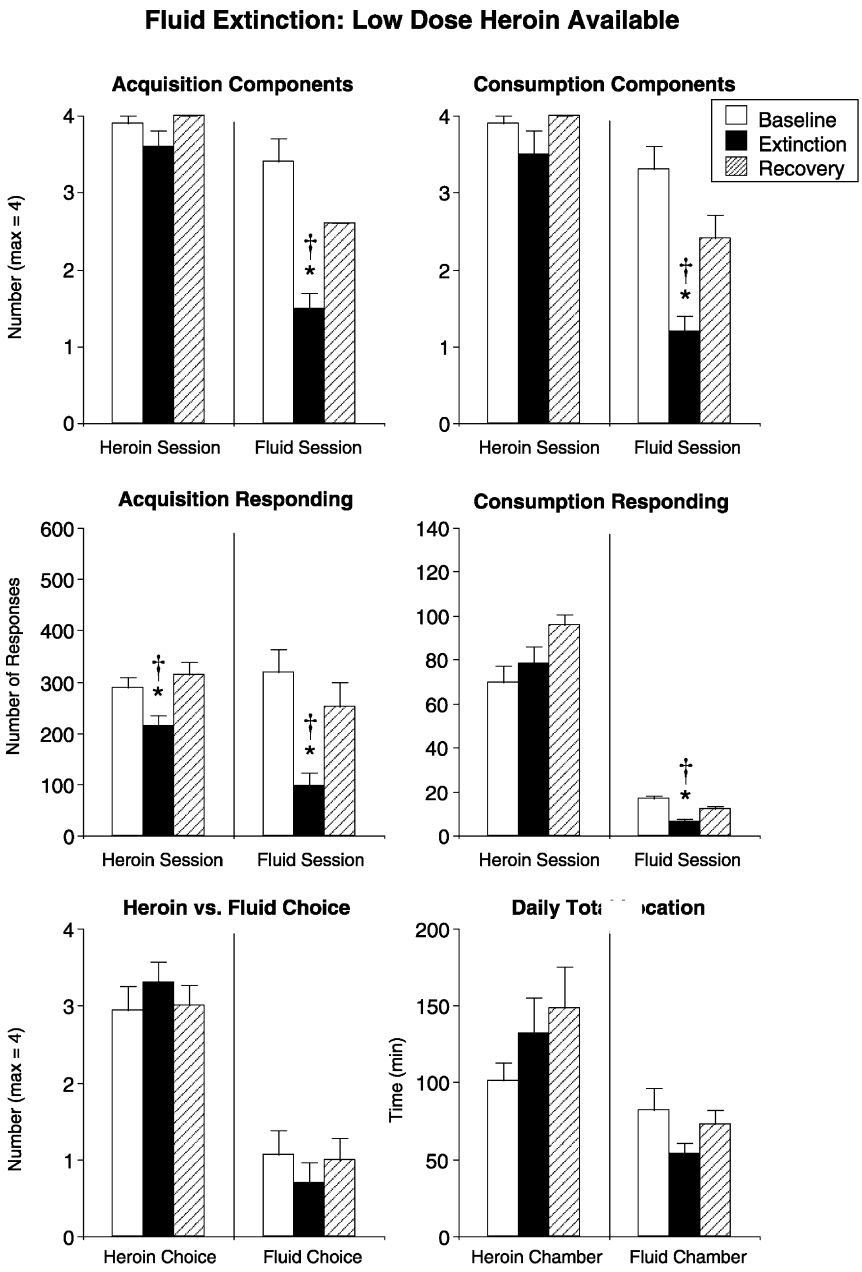

Fig. 4. Responding during heroin and fluid sessions, and choice and location preference as a function of fluid extinction when the low-dose (0.3 mg/kg) heroin was available (see Fig. 1 for details).

chambers (83 min) throughout the day. However, during fluid extinction, the amount of time spent in the heroin chamber increased while the amount of time spent in the fluid chamber decreased [$F(1,2)=7.3$, $P<.04$] and this location preference for the heroin chamber persisted even after fluid was reinstated [$F(1,2)=7.0$, $P<.04$]. During fluid sessions, monkeys spent significantly more time in the fluid chamber than the heroin chamber at baseline [$F(1,2)=7.4$, $P<.04$], but during fluid extinction, monkeys decreased the amount of time spent in the fluid chamber. During heroin sessions, animals consistently spent significantly more time in the heroin chamber relative to the fluid chamber, regardless of the fluid condition.

4. Discussion

The results of the present study show that (1) smoked heroin was reliably self-administered by nonopioid-dependent adult male rhesus monkeys; (2) these doses of smoked heroin were reliably chosen over the concentration of sweetened fluid tested; (3) monkeys usually had a location preference for the chamber where smoked heroin was self-administered; (4) there was modest evidence from some measures that the effects of smoked heroin were dose-related; and (5) during heroin extinction, several measures of commodity seeking shifted from heroin to fluid, such as increased acquisition responding for fluid, increased number

of fluid choices, and a shift in location preference to the fluid chamber.

The present findings extend the two other studies that have investigated smoked heroin self-administration in laboratory animals. Mattox and Carroll (1996) demonstrated that smoked heroin was self-administered over a wide dose range (0.1–1.6 mg/kg) and that when a peripherally acting opioid loperamide was substituted for heroin, self-administration decreased and extinction criteria were met within 8–15 days, and responding returning to baseline levels in 1–20 days. In a previous study (Foltin and Evans, 2001a) using some of the same monkeys and similar procedures as in the present study, smoked heroin was delivered via a powder, and extinction testing was conducted by having smoking trials continue as before (with all of the stimuli associated with heroin delivery), but no drug was delivered and animals simply sucked warm air. Extinction criteria were met within 3–6 days, and responding returned to baseline levels in 1–3 days. In the present study, heroin was dissolved in ethanol; thus, an active vehicle was delivered during extinction testing, again with all of the stimuli associated with heroin delivery. Extinction criteria were met within 6–16 days and responding typically returned to baseline levels in 1–4 days. The more rapid extinction in our previous study (Foltin and Evans, 2001a) is probably due to the fact that warm air, rather than an active vehicle, was used. Nevertheless, all three studies were able to maintain reliable heroin self-administration and to extinguish heroin responding when heroin was removed, thus providing clear evidence that smoked heroin can function as a reliable reinforcer in nondependent rhesus monkeys.

The purpose of the present study was to assess how three measures of heroin seeking (i.e., choice behavior, location preference, and acquisition responding during the first component of the second-order schedule) would vary when an alternative nondrug reinforcer was available and during heroin extinction. One measure of heroin seeking was the number of heroin choices over the number of fluid choices. The majority of previous studies that have modified drug-reinforced behavior with nondrug alternative reinforcers have used concurrent or discrete-trial choice procedures (Nader and Woolverton, 1991, 1992; Carroll et al., 1989, 1991; Comer et al., 1994; Rawleigh et al., 1996). When either dose of heroin was available, heroin was reliably chosen over sweetened fluid on 3.5 out of the four choice trials. However, when either dose of heroin was replaced with the vehicle (heroin extinction), choice behavior shifted from heroin to fluid, and when heroin was reinstated, the choice of heroin over fluid returned to baseline levels. In contrast, when water was substituted for the sweetened fluid (fluid extinction), there were no changes in the choice of the high dose of heroin, but when the low dose of heroin was available, there was a small increase in heroin choice. Thus, the choice measure of heroin seeking was sensitive to heroin extinction. The failure to see increases in heroin choice during fluid extinction was probably due to the limited number of choice opportunities since animals were already choosing heroin on 3–3.5 of the four choice opportunities.

How much time monkeys spent in the heroin-associated chamber was our location preference measure of heroin seeking. Although the location preference measure used in the present study is similar to CPP, it is important to note that it is not the same as CPP (e.g., Schechter and Calcagnetti, 1993; Bardo et al., 1995). In place-preference training, drug is usually administered noncontingently to animals confined to one test environment; the animals do not live in the test chambers; the conditioning and testing trials are relatively short; and the preference is recorded in the absence of drug. In this procedure, animals had the ability to move from chamber to chamber throughout the day, and location was recorded while animals were experiencing drug effects, at least part of the time. In the present study, throughout the day, monkeys spent more time in the heroin chamber than in the fluid chamber (i.e., they had a location preference for the heroin chamber). The only condition for which this was not the case was at baseline when the low dose of heroin and fluid were available, indicating that location preference varies depending on the reinforcing efficacy of the drug available. Further, location preference for the heroin chamber was sensitive to heroin availability such that during heroin extinction, location preference for the heroin chamber decreased, with a corresponding increase in time spent in the fluid chamber. Yet, location preference (based on total time throughout the day) for the heroin chamber did not recover to baseline levels within the first few days after heroin was reinstated. The reasons for this are unclear, but in all cases, the location preference for the heroin chamber reemerged after several additional days. However, location preference during heroin sessions rapidly returned to baseline levels when heroin was reinstated, suggesting that total daily location preference cannot be solely accounted for by time spent responding during heroin sessions. During fluid extinction, a different profile was observed. When the high dose of heroin was available and water was substituted for fluid, there was no change in the location preference for the heroin chamber; it remained high. However, when the low dose of heroin was available and water was substituted for fluid, location preference for the heroin chamber tended to increase. These results extend previous findings from this laboratory that have demonstrated location preferences induced by orally self-administered cocaine (Foltin and Evans, 1997, 1999), smoked heroin (Foltin and Evans, 2001a), and food (Evans and Foltin, 1997). Similarly, several studies using the CPP have demonstrated that time spent in a drug-paired environment is sensitive to extinction (Bardo et al., 1984; Calcagnetti and Schechter, 1993; Mueller and Stewart, 2000).

The utility of second-order schedules is that they allow one to differentiate between the motivational effects (seeking behavior that occurs prior to drug administration) and the direct reinforcing effects of the drug (taking behavior; see Goldberg et al., 1976; Markou et al., 1993; Arroyo et al.,

1998). In addition, the stimuli associated with drug availability during the acquisition component of a second-order schedule become conditioned stimuli that acquire incentive motivational effects that are thought to play an important role in the initiation, maintenance, and reinstatement of drug-seeking behavior (Markou et al., 1993; Arroyo et al., 1998). Further, the presence of these conditioned stimuli during the first component is critical for maintaining high rates of responding over relatively long time intervals before drug administration. Thus, responding during the first (acquisition) component of the second-order schedule served as another measure of drug-seeking behavior before actual drug administration. In the present study, when the high dose of heroin was available, the number of acquisition components completed was greater for heroin than for fluid. Correspondingly, the number of acquisition responses tended to be greater during high-dose heroin sessions than during fluid sessions, whereas when the low dose of heroin was available, the numbers of heroin and fluid acquisition responses were similar. In addition, the number of acquisition responses during heroin sessions tended to be greater when the high dose of heroin was available than when the low dose of heroin was available. These findings indicate that under baseline conditions, the high dose of heroin tended to be more reinforcing than sweetened fluid and was modestly more reinforcing than the low dose. More importantly, when the high dose of heroin was replaced with vehicle, the number of fluid acquisition responses *during fluid sessions* significantly increased even though these sessions occurred after heroin sessions. Similarly, when the low dose of heroin was replaced with vehicle, the number of fluid acquisition responses also increased, but not significantly. A previous study by Campbell and Carroll (2000) showed that when saccharin, rather than water, was available for consumption during the intersession period, oral PCP consumption significantly decreased during PCP self-administration sessions. Taken together, these findings suggest that during extinction of one reinforcer, responding for an alternative reinforcer can be modified even when the alternative is not concurrently available.

Although not a direct measure of heroin seeking, the number of inhalations during the consumption component of heroin sessions was larger when the high dose of heroin was available than when the low dose of heroin was available (mean of 117 vs. 71 inhalations, respectively; $P<.07$). Lastly, monkeys took longer to extinguish responding when the ethanol vehicle was substituted for the high dose of heroin compared to the low dose of heroin (11.5 vs. 7.5 days, respectively; $P<.036$). These data, along with the heroin acquisition responding, suggest modest differences between the two doses of smoked heroin tested.

There are several possible reasons why greater differences were not observed between the two heroin doses. Two obvious explanations are that a small range of heroin doses was tested and a small number of animals were tested. However, another possible explanation is that a second-order schedule of reinforcement was used. Although second-order schedules have a number of advantages (see above), these schedules do have several limitations, including limited sensitivity to manipulations of the reinforcer magnitude, such as drug dose or amount of food, even over a wide range, in part due to the high rates of responding engendered by second-order schedules such that rate of responding is minimally affected by dose (Goldberg et al., 1976; Sanchez-Ramos and Schuster, 1977).

In the present study, most—but not all—measures (e.g., the number of consumption components and consumption responses during fluid sessions; see Fig. 3) fully returned to baseline levels during recovery. This could also be a result of using a second-order schedule of reinforcement that results in high rates of responding. When Carroll (1985) compared oral PCP-maintained behavior under three different schedules of reinforcement, responding under the second-order schedule was higher when water was substituted for PCP, and was more resistant to extinction compared to the tandem or FI schedules. In addition, the presence of brief conditioned stimuli associated with reinforcement also plays an important role in initiating, maintaining, and reinstating responding for drug. Arroyo et al. (1998) showed that when extinction testing was conducted in rats without presenting the conditioned stimuli, responding decreased to lower levels than for the group of rats that had the conditioned stimuli present during extinction. Furthermore, responding did not fully return to baseline levels during reinstatement in the group that had the conditioned stimuli present during extinction. In the present study, all of the stimuli associated with reinforcement were present during extinction testing, which could in part account for the delay in some measures returning to baseline levels.

While heroin extinction resulted in clear changes in both heroin-maintained behavior and fluid-maintained behavior, fluid extinction did not substantially alter heroin-maintained behavior. This may have been due to the low reinforcing effects of the sweetened fluid. Evidence for this is that when the high dose of heroin was available, reinstatement of fluid following fluid extinction did not result in a full recovery of fluid responding to baseline levels. In addition, there were no changes in either choice or location preference as a function of the fluid condition when the high dose of heroin was available. However, when the low dose of heroin was available and water was substituted for the sweetened fluid, there were small increases in heroin consumption responding, heroin choice, and time spent in the heroin chamber. In fact, the number of heroin consumption responses and the time spent in the heroin chamber remained elevated even after fluid was reinstated. These findings are somewhat consistent with a study conducted by Carroll et al. (1989) in rats who self-administered intravenous cocaine and had concurrent access to a glucose+saccharin (G+S) solution. In that study, when water was substituted for G+S, cocaine responding increased and G+S responding decreased, but

when G+S was reinstated, neither cocaine responding nor G+S responding returned to baseline levels. That study also showed that when cocaine was removed, G+S responding also decreased in those animals with a high intake of G+S, whereas for those animals with a low intake of G+S (weak reinforcer), cocaine extinction increased G+S intake and it remained high even when cocaine was reinstated. Thus, another possibility is that greater changes would have been observed in the present study if animals had more smoking and fluid trials, as well as choice opportunities each day.

The present study had several limitations. A small range of heroin doses was tested and animals were restricted in the number of doses they could self-administer (maximum of eight if they chose heroin over fluid on all four choice trials to avoid opioid dependence). Also, a noninvasive measure was used to verify that monkeys were inhaling the smoked heroin (i.e., opioid levels were measured in urine), but there was no control for urinary volume or concentration. The fact that urinary morphine levels were not consistently dose-related may have been due to several factors, including the crude method used to measure opioid levels or variability in inhalation depth and inhalation duration, which were not measured. Another limitation is that the magnitude of the alternative reinforcer, sweetened fluid, was not manipulated by either delivering a greater volume or altering the sweetness of the fluid. Lastly, a relatively modest reinforcer (sweetened fluid) was used instead of a more efficacious reinforcer, such as candy (Foltin and Evans, 2001b). It is possible that if candy had been used as the alternative reinforcer, a more pronounced dose–response function with heroin may have been observed.

In conclusion, smoked heroin is an efficacious reinforcer in nonopioid-dependent rhesus monkeys and three different measures of heroin seeking can be modified by heroin extinction and the presence of a modestly reinforcing nondrug alternative. Previous studies have shown that motivation for heroin taking can be enhanced by an increased access to heroin exposure (Ahmed et al., 2001). The strength of this model of smoked heroin is that it can be used to study how these various measures of heroin seeking, that can be assessed simultaneously in the same animals, are modified in animals with greater access to heroin use, up to levels that produce physical dependence. Ultimately, this will provide a better understanding of the relationship between drug-seeking behavior and drug-taking behavior.

Acknowledgements

This research was supported by DA-08460 from The National Institute on Drug Abuse, and approved by the New York State Psychiatric Institute Animal Care and Use Committee. The assistance of Julian Perez, Rafael Salazar, Nicole Cain, Asiyah Rehman, and Dr. Mohamed Osman is gratefully acknowledged.

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