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Withdrawal from a self-administered or non-contingent cocaine binge: differences in ultrasonic distress vocalizations in rats

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Abstract After termination of a self-administered cocaine "binge," rats emit ultrasonic vocalizations (USVs) and these calls may represent affective distress. The present study investigated whether the rates of USVs as indices of withdrawal from a period of continuous access, depends on cocaine being *self*-administered versus given non-contingently. Five days after implantation of a jugular catheter, triads of rats that were matched for housing, food-training and surgery were placed into experimental chambers. The active rats were allowed to acquire self-administration of cocaine (0.5 mg) while the two yoked animals passively received either cocaine (0.5 mg) or saline according to the active animal's pattern of administration. Once the active animal responded at a stable rate over 3 days, with every third lever press being reinforced by cocaine (FR3), it was allowed free access to cocaine (0.5 mg) for 16 h. Subsequently, all animals were exposed to 18 air puffs (10 psi) at 0, or 1, 3, 5, 7 and 14 days after the "binge". Immediately following the binge, there was no significant difference in the rate of startle-induced USVs between the active cocaine group and the yoked saline group. However, the yoked or non-contigent cocaine rats emitted significantly higher rates of USVs immediately after the last cocaine infusion. At the time of the peak increase in USVs, the active and yoked cocaine groups were significantly different. For up to 5 days after unlimited cocaine access, the active and passive-cocaine groups showed an increase in USVs response when compared to the yoked saline group. The emerging increase in USVs and their gradual decline observed after termination of a cocaine "binge" can be interpreted as an abstinence phenomenon. The non-contingent cocaine appears to be highly aversive, as indicated by the immediate significant increase in the rate of USVs after termination of a cocaine "binge".

Key words Cocaine · Ultrasound · Vocalization · Withdrawal · Non-contingent · Self-administration · Reinforcement · Anxiety · Stimulant · Binge · Intravenous · Triads

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Introduction

The contingency between a behavioral response and cocaine delivery is an essential criterion for this drug to be considered a reinforcer (Balster et al. 1976; Fischman and Schuster 1982). Cocaine is such a powerful reinforcer that animals, including humans, will repeatedly self-administer large doses of cocaine over a long period of time (Deneau et al. 1969; Gawin and Kleber 1986). An important feature of this prolonged self-administration or "binge," is that other life activities are abandoned and drug intake can become the sole focus (Gawin and Kleber 1986; Gawin 1991). In fact, rhesus monkeys will self-administer cocaine to the point of death (Johanson et al. 1976).

The principle of contingency, as it links cocaine delivery and behavior, highlights the importance of control and predictability. The importance of contingency between the behavior and the cocaine delivery is demonstrated when this relationship is removed. For example, control over IV infusions of cocaine doubles the lethal dose when compared to animals that received the drug passively (Dworkin et al. 1995b). Similarly, dopamine levels are significantly increased after

self-administered cocaine but not after passively administered drug (Wilson et al. 1994). The unpredictable nature of inescapable, non-contingent drug-delivery may also act as a stressor (Barry and Buckley 1966).

Feelings of loss of control and predictability are major psychological variables that contribute to stress and anxiety (Sapolsky 1996). Stress and anxiety have been proposed to be involved in the etiology of psychostimulant abuse and to contribute as primary symptoms to depression during cocaine withdrawal (Piazza et al. 1990; Maccari et al. 1991). Many environmental stressors have been shown to affect acquisition and maintenance of cocaine self-administration (Piazza et al. 1990; Hooks et al. 1992). For example, social stress enhances acquisition of cocaine self-administration and causes perseverative responding on the reinforced lever at low and intermediate maintenance doses of cocaine (Miczek and Mutschler 1996; Tidey and Miczek 1997). Non-contingent footshock, in which the animal receives inescapable and unpredictable shock, also facilitates acquisition of cocaine self-administration and relapse (Goeders and Guerin 1994; Erb et al. 1996). Although it appears that these types of stressors affect cocaine administration, very little is known about their effects on cocaine withdrawal.

Clinical studies have shown that one of the most commonly observed symptoms of cocaine withdrawal is extreme anxiety (Gawin and Kleber 1986; Weddington et al. 1990). Patients that have terminated continuous cocaine use have a significantly higher level of anxiety for up to a week when compared to controls (Weddington et al. 1990). Apparently, the peak in anxiety is early in the short- term abstinence period or withdrawal phase (Gawin and Kleber 1986; Weddington et al. 1990). One proposal specifically characterizes this peak in anxiety as the "crash" phase of cocaine withdrawal which occurs between 1–3 days after termination of drug (Gawin and Kleber 1986).

Although symptoms of anxiety during short-term abstinence have been clinically defined, an appropriate animal model, characterizing this peak in anxiety, remains elusive. Nonetheless, there have been several investigations of the behavioral consequences of cocaine withdrawal in rats and monkeys. Termination of cocaine can disrupt ongoing operant behavior, intensify the effects of punishment on licking and increase intracranial self-stimulation (ICSS) thresholds (Carroll and Lac 1987; Woolverton and Kleven 1988; Fontana and Commissaris 1989; Markou and Koob 1991). One interpretation attributes these behavioral changes after termination of cocaine to anhedonia (Markou and Koob 1991; Koob 1995).

Ultrasonic vocalizations (USVs) may possibly represent a more direct measure of emotional changes during cocaine withdrawal (Miczek et al. 1995). In fact, startle-induced USVs increase after termination of both oral and intravenous (IV) self-administered cocaine (Barros and Miczek 1996; Mutschler and Miczek 1998). Because specific types of USVs are directly associated with anxious states and have been used in the study of withdrawal from other drugs such as morphine and diazepam, startle-induced USVs after termination of cocaine may be relevant to the anxiety that is clinically observed (Vivian and Miczek 1991; Miczek and Vivian 1993).

The increase in anxiety that is observed during the "crash" is most often associated with the "binge" pattern of drug intake. It is possible to model different aspects of the human binge in animal studies. For example, multiple injections that are closely spaced in time have been employed to mimic the repeated nature of drug administration during a binge (Maisonneuve and Kreek 1994; Maggos et al. 1996, 1997). Using an IV self-administration methodology, which resembles contingent human self-administration, other procedures allow animals to self-administer or "binge" on cocaine continuously for different lengths of time (Markou and Koob 1991; Mutschler and Miczek 1998). One important feature of this self-administered "binge" is that animals, like human addicts, will continually press a lever that is reinforced with cocaine for up to approximately 16 h, while all other activities such as eating, drinking, and sleeping are abandoned (Mutschler and Miczek 1998). The objective of the present study was to examine the differences between withdrawal from cocaine, as measured by tactile startle-induced USVs, that is *self*-administered in a binge-like pattern versus cocaine that is given independently of any behavioral actions, i.e. without any contingency between a specific behavior and cocaine delivery.

Materials and methods

Animals

Subjects were male Long-Evans rats (Charles River, Wilmington, Mass., USA), weighing 320–350 g at the beginning of the experiment. The rats were housed individually in hanging, stainless steel cages in a vivarium with a reversed light cycle (12 h:12 h, lights on at 0800 hours, 35–40% humidity, 21 ± 1°C), with free access to water and food (Purina laboratory chow). The animals were grouped into triads, i.e. three rats were treated as a single experimental unit and matched for food restriction, training, surgery and other experimental procedures.

Training

After acclimation to the laboratory, animals were food restricted to 85% of their original body weight. They were then placed in an operant chamber ($30 \times 26 \times 31.5$ cm) and trained to press a lever until they responded reliably, with every third lever press being reinforced with 0.1 ml of a 50:50 solution of condensed milk and water. Once all three animals were trained, usually within less than a week, the animals were given free access to food and water until they all reached a minimum of 350 g body weight.

Surgery

All animals within the triad received permanently indwelling catheters (Silastic silicon tubing, ID 0.64 mm, OD 1.19 mm; VWR Scientific, Bridgeport, N.J., USA) implanted into the right jugular vein (Remie et al. 1990) on the same day. The catheter was threaded subcutaneously over the shoulder between the scapulae and through an incision in the scalp. Once the catheter was attached to a plastic pedestal (Plastics One, Roanoke, Va., USA) and capped, the pedestal was secured to the skull with dental cement that was anchored to stainless steel screws (Small Parts, Inc., Miami Lakes, Fla., USA). Rats recovered from surgery for 5 days in stainless steel hanging cages with free access to food and water, and were then moved to self-administration operant chambers, as previously described (Mutschler and Miczek 1997). Briefly, the animals were permanently housed in identical self-administration polycarbonate chambers ($30 \times 30.5 \times 24.5$ cm) with a stainless steel tray covered with wood shavings, illuminated by a 7-W white bulb, and enclosed in a light- and sound-attenuating box. The catheter was flushed daily with heparinized saline (20 IU/ml; 4 IU/0.2 ml per day) and brief pulses of saline were given (0.17 ml/30 min) overnight in order to maintain the catheter's patency and sterility.

Cocaine self-administration

Both the experimental chamber and the outer enclosure had a hole in the ceiling to allow free movement of the tethered catheter (Plastics One) that was connected via a counterbalanced swivel to an infusion pump (Med Associates). One wall of the chamber accommodated interchangeable panels. One panel was equipped with two levers each 5 cm from the floor with a red cue light above the active lever and a green cue light (both 4 W) in the middle of the panel. The alternate panel provided access to a water bottle.

All animals were exposed to tactile startle stimuli immediately prior to the first test session. Specifically, animals were exposed to a 4-min habituation period, 18 air puffs at 10 psi occurring 25–35 s apart over 8 min, and a 4-min post-test period. Only one rat (the active cocaine rat) was allowed to acquire self-administration of cocaine. The other two rats of the triad were yoked such that they passively received either cocaine (0.5 mg/infusion) or saline according to the active rat's pattern of self-administration (Dworkin et al. 1995a,b). During daily test sessions, all three animals had panels equipped with levers and cue lights. Lever presses of both the yoked cocaine and saline controls were counted, but they were of no consequence. During the active rat's acquisition, each lever press resulted in one infusion of 0.5 mg/0.1 ml cocaine over 5.6 s, corresponding to approximately 0.5 mg/infusion. Since animals weighed on average 400 g, this corresponds to approximately 1.25 mg/kg. Acquisition was defined as obtaining 15 reinforcements usually within a 3-h session on 2 consecutive days, with each lever press being reinforced. Throughout the rest of the experiment, every third lever press (fixed ratio, FR3) was reinforced by a cocaine infusion. The start of the session was signaled by switching on the green cue light and activating the syringe pump to fill the catheter with drug. Each 5.6-s infusion was accompanied by illumination of the red light above the active lever. At the end of the infusion, both cue lights were turned off during a 30-s time out period, after which the green cue light was switched on again to signal the availability of drug. Lever presses on the inactive lever were counted, but were of no consequence. The cue lights in the yoked boxes were illuminated as presented to the active rat. The experimental session terminated after the experimental rat was reinforced by 15 infusions of cocaine or after 3 h, whichever came first. All events were controlled and data were collected via a PC-controlled interface and software package (Med Associates).

Experimental design

Once the active cocaine animals responded at a stable rate on an FR3 schedule for 3 consecutive days they were allowed continuous access to cocaine (0.5 mg/infusion) for 16 h. During this time both yoked controls continued to receive passively either cocaine (0.5 mg/infusion) or saline according to the active rat's pattern of administration. This continuous access period was defined as a "binge." Subsequently, all animals were exposed to eighteen 10 psi air puffs immediately after termination of the continuous access, or 1, 3, 5, 7 and 14 days after the last cocaine infusion of the continuous access, and their reflexes and USVs were measured.

Apparatus

Startle

Startle stimuli were controlled and responses were recorded by a PC using the SR-LAB startle response system (San Diego Instruments). The system included a clear acrylic cylinder (20 cm long; ID 8 cm) that was connected to an accelerometer which transduced the rat's movement into voltage changes. The startle apparatus was inside of a sound- and light-attenuating chamber.

Startle stimulus and measurement

Startle stimuli were bursts of compressed air delivered to the dorsal side of the animal through a copper pipe (0.4 cm in diameter) located 3 cm above the subject. Rats were placed into the startle chamber; after a 5-min habituation period, eighteen 50 ms air puffs at 10 psi were delivered every 25, 30, or 35 s. Startle amplitude was defined as the maximal accelerometer voltage (V_{max}) measured during a 200 ms recording window.

Ultrasound

USVs were detected with a 0.064 cm condenser microphone (Bruel and Kjaer Model 4135), preamplifier (B&K Model 2633), filter (Krohn-Hite Model 3550) and measuring amplifier (Bruel and Kjaer Model 2610). The condenser microphone was suspended 3 cm above the acrylic cylinder. Amplifier output was sent to: (1) an oscilloscope (Telequipment Model DM54) to allow visual verification of vocalizations and, (2) an automated MacIntosh II sound analysis system which determined the frequency and duration of all 15–35 kHz vocalizations that were longer than 0.075 s and separated by 0.05 s or more (Miczek and Vivian 1993).

Statistical analysis

USV data were expressed as medians because the data were not normally distributed. All other results were expressed as mean ± SEM and the criterion for significance was $P < 0.05$. The rate of ultrasonic vocalizations was analyzed using the Fisher Exact Probability test. Differences in the amount of weight loss after the "binge" were analyzed using a one-way ANOVA and the Tukey test for multiple comparisons versus the control group.

Results

The active cocaine rats acquired self-administration (0.5 mg/infusion) on average, in less than 3 days

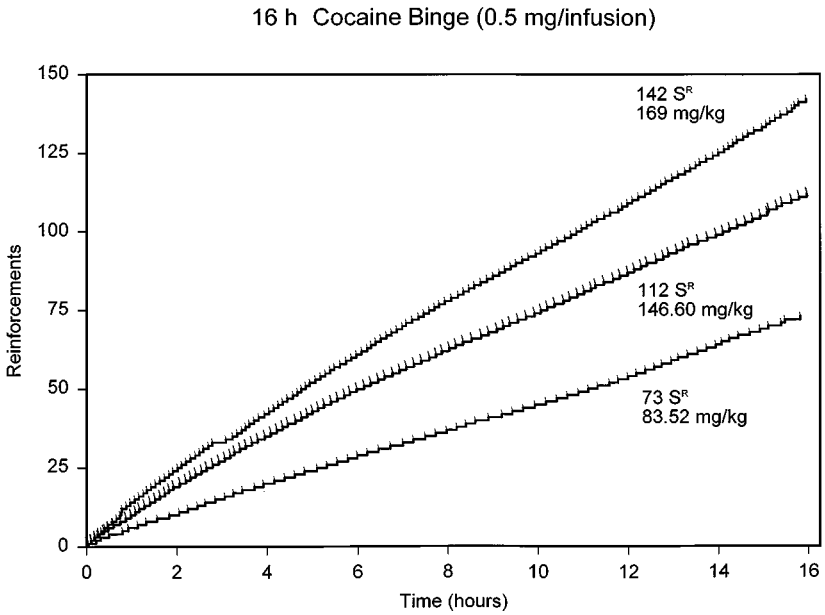

Fig. 1 Cumulative records of cocaine reinforcements from animals during 16 h of unlimited continuous access. The *middle record* is most representative of the group average intake of drug over the 16-h period. The *top record* is taken from the animal with the highest number of cocaine infusions and the *bottom record* represents the data from the animal with the lowest number of cocaine infusions. Each upward deflection represents an infusion of cocaine

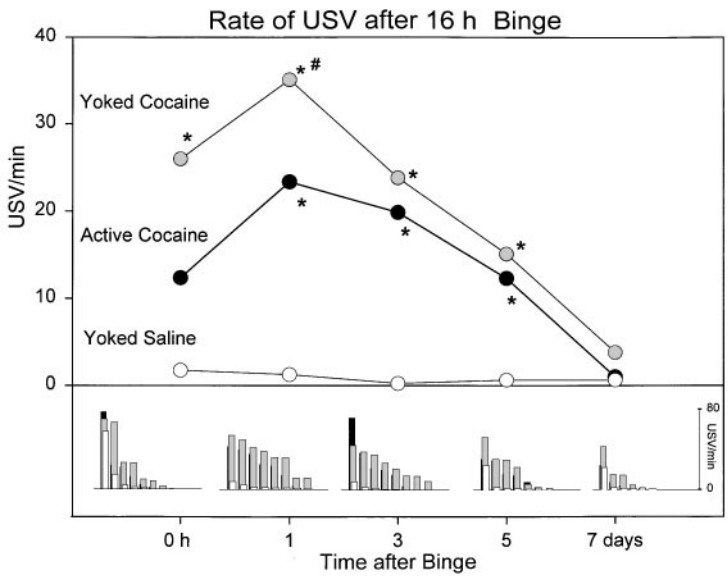

Fig. 2 The group medians for the rate of ultrasonic vocalizations after 16 h of continuous access to cocaine as a function of the time after the last drug infusion. The *bottom half* of the graph represents data from individual rats, in descending order of magnitude. The *white bars* represent individual animals in the yoked saline group, the *grey bars* represent individual animals in the yoked cocaine group and the *black bars* represent animals in the active cocaine group (*$P < 0.05$, in comparison with the yoked saline group; #$P < 0.05$, for the comparison between the active and yoked cocaine groups)

(2.55 ± 0.19). After ca. 1 week (7.23 ± 0.40 days), the active animals maintained stable response rates on an FR 3 schedule of reinforcement (0.34 + 0.01 resp./min.). At this time, the active animals were given continuous access to cocaine for 16 h. During the "binge," the active animals self-administered an average of 135.4 ± 5.7 mg/kg cocaine and the passive cocaine animals received an average of 134.7 ± 5.3 mg/kg of drug (see Fig. 1); these amounts of cocaine were not significantly different from each other. Figure 1 illustrates the regular pattern of administration during the entire 16-h period of continuous access. This regular continuous pattern is evidence that the animal did not sleep, and the water bottle and food were left untouched.

After termination of the continuous access to cocaine all animals were exposed to tactile startle stimuli and tested for rate of USVs at several time points after termination of access. Immediately after the last infusion of cocaine, the active cocaine rats' rate of USVs did not significantly differ from the saline control rats (Fisher Exact; $P = 0.53$). At later time points after the "binge", the active cocaine rats had a significantly higher rate of USVs than that of the saline control rats (Fisher Exact: 24 hr, $P = 0.001$; 72 h, $P = 0.03$; 5 days, $P = 0.03$; see Fig. 2).

The passive cocaine rats' rate of USVs was significantly different from the active cocaine rats' immediately after termination of the "binge" (Fisher Exact: 0 h; $P = 0.02$) and at 24 hours after the "binge"

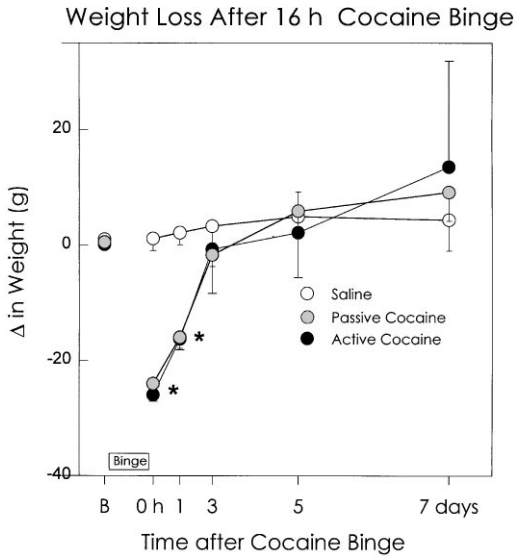

Fig. 3 The change in body weight of the active and yoked cocaine groups compared to the yoked saline group after exposure to 16 h of continuous access to cocaine or infusions of saline as a function of time after the continuous access period. At the 0-h time point, $n = 16$ and at all other time points $n = 8$. The *vertical bars* represent the SEM. The "Pre" on the x-axis represents the average body weight of each group at the beginning of the day of the "binge". The data point at "Pre" represents the beginning body weight for all three groups at this time point (*$P < 0.05$)

(Fisher Exact; $P = 0.05$). The passive cocaine rats were significantly different from the saline rats immediately after the "binge" and at several time points after termination of cocaine access (Fisher Exact: 0 h, $P = 0.05$; 72 h, $P = 0.03$; 5 days, $P = 0.05$; see Fig. 2).

At several time points after termination of continuous access, the active and passive cocaine groups had a significant amount of weight loss when compared to the saline group (see Fig. 3). Immediately after the "binge" there was a significant difference between groups ($F_{2,65} = 91.88$; $P < 0.001$), with the saline control rats significantly different from both the passive cocaine rats ($q = 15.73$; $P < 0.05$) and the active cocaine rats ($q = 17.45$; $P < 0.05$). The weight loss remained significant at 24 and 72 h after the "binge" (24 h: $F_{2,40} = 23.44$, $P < 0.001$; 72 h: $F_{2,21} = 4.13$, $P < 0.03$). In previous studies, 10 and 20 psi air puffs were used to elicit USVs and startle responses (Mutschler and Miczek 1998). The more intense stimulus (20 psi) did result in significant differences at more time points in startle reflex between animals that received cocaine and control animals. However, the 10 psi stimuli more readily separated the active cocaine and control groups in terms of the rate of USVs. In the present study, a 10 psi stimulus was used and there were no significant effects on startle parameters observed in the present study (see Table 1). This may be due to the decreased pressure of the air puff stimulus (Mutschler and Miczek 1998).

Table 1 The maximal startle response (V_{max}) for the active and yoked cocaine and yoked saline groups at 0, 24 and 72 h after the last cocaine infusion of a 16-h continuous access period

Group	V_{max}		
	0 h	24 h	72 h
Active cocaine	242.8 ± 51.1	336.3 ± 44.9	385.9 ± 69.8
Yoked cocaine	227.2 ± 19.3	306.4 ± 21.1	298.6 ± 57.2
Yoked saline	290.4 ± 48.2	292.4 ± 30.7	264.7 ± 37.6

Discussion

The present results demonstrate that after a 16 h self-administered "binge," the rate of tactile startle-induced USVs follows a time course that peaks 24 h after termination of cocaine access. It is important to note that these differences in withdrawal were only observed after probing the animal with a subtle stimulus such as the 10 psi air puffs. Previous studies have shown that a less intense stimulus (e.g. 10 psi versus 20 psi) more readily reveals differences in the rate of USVs between animals that are exposed to cocaine and control animals. However, a less intense air puff is less effective in eliciting a startle reflex that is enhanced in animals in which cocaine was withdrawn. This dissociation of the USVs and startle reflex suggests that the USVs are a separate consequence of the exposure to the air puff stimuli and are not directly associated with the startle reflex itself.

The large increase in anxiety-like vocalizations at 24 h after the last *self*-administered cocaine suggests that the increase in USVs was not the direct consequence of a large amount of cocaine. The yoked cocaine group emitted USVs following a time course that resembled the peak and decline of the self-administering animals. Interestingly, this group of rats that received non-contingent cocaine began to emit USVs at a higher rate immediately after termination of continuous access. The heightened rate of USVs in the yoked group may imply that the aversive effects of passive administration of the very large cocaine doses immediately caused an increase in the USVs. Furthermore, this enhancement persists for several days after termination of cocaine.

Differences between contingent and non-contingent cocaine are not altogether surprising since the reinforcing effects of this drug have been shown to depend on the behavioral context rather than on its inherent pharmacological properties (Barrett 1987). It remains important to emphasize that psychostimulant drugs such as cocaine or nicotine may function as positive reinforcers, i.e. maintain operant behavior that is reinforced by infusion of the drug. However, the same dose of these drugs can be negatively reinforcing, i.e. maintain operant behavior that postpones an infusion of the drug (Spealman 1979, 1983). Similarly, animals that

had acquired IV self-administration of amphetamine, later learned to avoid the taste of a sweet solution that was associated with experimenter-administered amphetamine (Wise et al. 1976). These findings suggest that there are fundamental differences between contingent and non-contingent drug delivery on operant behavior. Self-administered psychostimulants can act as positive reinforcers, and experimenter-administered drugs function as negative reinforcers or punishers. In fact, non-contingent delivery of cocaine results in a higher rate of mortality than contingent delivery of the same dose of drug (Dworkin et al. 1995b). The issue of behavioral control over drug intake has also been highlighted in carefully designed studies with morphine and ethanol (Mello and Mendelson 1970; Siegel 1988).

In the present study, individual differences in the response to passive- and self-administered cocaine were observed. A few rats in both the active and yoked cocaine groups emitted USVs to a lesser degree than was characteristic for the entire group. Although the etiology of these individual differences was not studied here, an investigation of this phenomenon may help to elucidate why there is a significant amount of variability between individuals in several aspects of cocaine use (Gawin and Kleber 1986; Piazza et al. 1990). Clinical studies describe at least two common patterns of cocaine intake. Some cocaine addicts self-administer the drug at high doses on a daily basis, while other addicts administer the drug in long duration binges that can last for several days (Gawin and Kleber 1986; Gawin 1991). However, the "crash" or short term abstinence syndrome is most often associated with binge pattern cocaine intake (Gawin and Kleber 1986; Gawin 1991). For this reason, the present study focused on tactile startle-induced USVs after binge-like cocaine self-administration. It is noteworthy that similar effects on tactile startle-induced USVs were observed after termination of daily intake of oral cocaine (Barros and Miczek 1996).

In addition to behavioral differences after termination of passive- and self-administered cocaine, withdrawal from contingent and non-contingent cocaine results in different and sometimes opposite neurochemical changes in the mesocorticolimbic monoamine systems (Wilson et al. 1994; Dworkin et al. 1995a). Results from ongoing molecular studies suggest that active and yoked cocaine groups differ in the way *zif* 268, an immediate early gene, is expressed in the prefontal cortex , nucleus accumbens and the VTA at various time points in withdrawal (Mutschler et al., in preparation). These results along with the presently observed behavioral findings, strengthen the hypothesis that the termination of cocaine self-administration results in a short-term abstinence phenomenon that can be quantified with anxiety-like vocal responses and concurrent molecular changes in mesocorticolimbic structures. The brief time course of the weight loss in both the active and passive cocaine group also suggests a short-term disturbance due to termination of cocaine access (see Fig. 3).

Converging evidence from the present results and previous studies shows that tactile startle-induced USVs can be used to quantify those aspects of withdrawal from cocaine that are relevant to emotional distress in humans (Miczek et al. 1995; Mutschler and Miczek 1998). Clinically, it is observed that the tendency to relapse during withdrawal is often highest when the negative withdrawal symptoms are at their worst (Jaffe 1970; Fischman and Schuster 1982). An important further criterion for considering the heightened USVs as indices of withdrawal is to reverse these effects by administration of the very drug from which animals are withdrawing. Recent data indicate that the withdrawal ultrasonic vocalizations can be reversed by renewed access to cocaine (Mutschler, Casadesus and Miczek, in preparation).

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