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Reinstatement and spontaneous recovery of nicotine seeking in rats

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Abstract Reinstatement and spontaneous recovery of previously extinguished nicotine-taking behavior were examined in rats. Male subjects were trained to self-administer nicotine (30 μg/kg per infusion, IV; one 60-min session per day for 3 weeks). Extinction sessions were then given for 5–10 days during which saline was substituted for nicotine. Subsequently, in the first set of tests for nicotine seeking, the reinstatement of lever presses that previously delivered nicotine was examined after priming injections of saline and nicotine (75, 150 and 300 μg/kg, SC; and 30 and 60 μg/kg, IV). In the second set of tests for nicotine-seeking, rats were tested after an additional 21-day drug-free period during which they were not exposed to the self-administration chambers (a test for the spontaneous recovery of drug seeking), and after priming injections of nicotine (150 and 300 μg/kg, SC). Reinstatement of extinguished food-reinforced behavior after exposure to nicotine was also determined. Priming injections of nicotine reinstated nicotine seeking regardless of the route of administration. In addition, previously extinguished nicotine seeking recovered spontaneously after a 21-day period during which rats were not exposed to the drug-taking environment. Nicotine also reinstated extinguished food-reinforced behavior in rats with a history of nicotine self-administration, but not in drug-naive rats. The present results extend previous work with opioid and stimulant drugs on reinstatement of drug seeking by the self-administered drug. It also appears that, as with other positive reinforcers, the mere passage of time is a sufficient condition for the spontaneous recovery of extinguished nicotine seeking.

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Introduction

High rates of relapse are common in former cigarette smokers and other drug users (Hunt et al. 1971; US-DHHS 1988; Carmody 1992). One factor that contributes to the relapse to drug use in humans, including tobacco use (Chornock et al. 1992), is acute re-exposure to the drug after a period of abstinence (Ludwig et al. 1974; Meyer and Mirin 1979; Jaffe et al. 1989; de Wit 1996). An animal model used to study this phenomenon is the reinstatement procedure; this procedure is regarded as a suitable method to study relapse (Stewart and de Wit 1987) and craving (Markou et al. 1993) processes. Reinstatement refers to the resumption of a previously extinguished conditioned response after acute non-contingent exposure to the unconditioned stimulus (Catania 1992). In the reinstatement model, the effect of acute, non-contingent re-exposure to drugs on the reinstatement of drug seeking is examined after training for intravenous (IV) self-administration of drugs and subsequent extinction of the drug-reinforced behavior (Stewart and de Wit 1987). Using this procedure, investigators have shown that priming injections of opioid and stimulant drugs reinstate extinguished drug seeking in drug-free rats and monkeys (Stretch et al. 1971; Gerber and Stretch 1975; de Wit and Stewart 1981, 1983; Shaham et al. 1994; Carroll and Comer 1996; Self et al. 1996).

In recent years, several laboratories reported that IV nicotine maintains stable self-administration behavior in rats (Corrigall and Coen 1989; Donny et al. 1995; Tessari et al. 1995; Epping-Jordan et al. 1996; Shoaib et al. 1996, 1997; but see Dworkin et al. 1993; Bozarth and Pudiak 1996). As with other drug or non-drug reinforcers, therefore, priming injections of nicotine would be expected to reinstate extinguished nicotine-taking behavior. One recent study examined the effect of priming in-

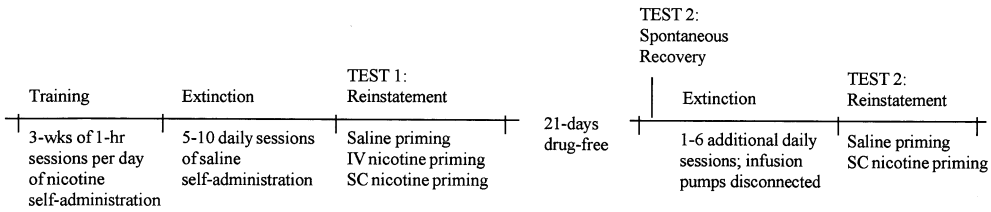

Fig. 1 Time line of experiment 1

jections of nicotine on reinstatement of nicotine seeking (Chiamulera et al. 1996). It was found that extinguished operant responding that was previously reinforced by nicotine was increased slightly by priming injections of nicotine. However, unlike the reinstatement of heroin and cocaine seeking by those drugs, respectively, nicotine reinstated drug seeking at doses that were much lower than the self-administered dose and the magnitude of the reinstatement effect was lower than that commonly observed with opioid and stimulant drugs. Thus, the data of Chiamulera et al. (1996) suggest that the reinstatement phenomenon with nicotine is qualitatively different from the reinstatement observed with opioid and stimulant drugs.

One rationale for the present experiments, therefore, was to re-examine this issue. First, we tested the effect of priming injections of nicotine on reinstatement of nicotine seeking using both the IV and the subcutaneous (SC) route of administration. Second, we have examined the issue of spontaneous recovery of extinguished responding for nicotine. Spontaneous recovery refers to the resumption of the extinguished conditioned response that occurs after time has passed following the conclusion of extinction. This phenomenon has been documented to occur with behaviors previously controlled by both appetitive and aversive reinforcing events (Bouton and Swartzentruber 1991), but it has not been systematically studied in the context of relapse to drug use. Thus, we tested whether rats would resume extinguished operant responding previously reinforced by nicotine after 21 days during which they were not exposed to the drug environment. Finally, for comparison purposes, we tested the effect of nicotine on the reinstatement of extinguished food-reinforced behavior in both nicotine-naive and nicotine-experienced rats.

Materials and methods

Subjects

The subjects were male Long-Evans rats (Charles River, Quebec; 300–350 g). Animals were housed in the animal facility in a reversed light-dark cycle (lights on between 1900 and 0700 hours). Prior to the start of the experiments, animals had free access to food and water. During the experiments, water was continuously available and the rats were fed 20 g chow (Purina Rat Chow) per day. Prior to undergoing surgery to implant IV catheters, rats were trained to press a lever for food in different operant boxes than the ones which would ultimately be used for IV self-administration. Procedures were as previously described (Corrigall and Coen 1989): rats were deprived of food for 24 h and were trained for several days to press a lever to receive 45 mg food pellets (P.J. Noyes Company Lancaster, N.H., USA) under a fixed-ratio 1 schedule of reinforcement (FR-1, each lever press is reinforced).

Surgery

Sixteen rats were anesthetized with a mixture of xylazine (Myles, Etobicoke, Ontario, Canada; 10 mg/kg, IP) and ketamine (MTC Pharmaceuticals, Cambridge, Ontario, Canada; 100 mg/kg, IP) and were surgically implanted with intravenous silastic catheters in the right jugular vein (see Corrigall and Coen 1989 for details). Penicillin G (Rogar/STB, London, Ontario, Canada; 300 000 IU; 0.2 ml/animal) was given at the time of surgery and buprenorphine (0.01 mg/kg, SC) was administered after the surgery. The catheters were flushed daily with 0.1 ml of a saline-heparin solution (30 U/ml; heparin was obtained from ICN Biochemical, Cleveland, Ohio, USA) and rats were allowed 6–7 days to recover from the surgery.

Drugs

Nicotine (Sigma, St Louis, Mo., USA) solutions (pH adjusted to 7.0) were prepared freshly each week. The unit dose for the IV nicotine self-administration was 30 μg/kg per infusion (all doses are expressed as the free base) with an infusion volume of 100 μl/kg and an infusion time of <1 s. Nicotine was also injected SC (75, 150 and 300 μg/kg) and IV (30 and 60 μg/kg) during tests for reinstatement; in these instances, the injection volume was 1 ml/kg.

Experiment 1: reinstatement and spontaneous recovery of nicotine seeking

The time line of experiment 1 is provided in Fig. 1.

Training and extinction of nicotine self-administration behavior

The nicotine self-administration procedure was similar to the one used in previous reports (Corrigall and Coen 1989; Corrigall et al. 1994). Drug self-administration was initiated on an FR-1 schedule of reinforcement with a 15-s timeout period after each drug infusion. During the timeout period, responses were recorded but did not lead to drug delivery; the timeout period was signalled by a light-tone stimulus combination. In the second week the response requirement was increased to FR-3 and in the third week to FR-5. Self-administration sessions (60 min per day; 5 days per week; Monday to Friday) were carried out in operant chambers equipped with two levers. Responses on one of the levers (the active lever) resulted in drug delivery when the schedule requirements were met, while responses on the other lever (the inactive lever, a measure of nonspecific activity) were recorded but were never reinforced. No priming injections were given during the training phase. Thirteen of the 16 rats acquired stable nicotine self-administration behavior. During the extinction phase, presses on the active lever resulted in saline infusions for eight rats with patent catheters. These rats were given priming injections of saline just prior to the start of each of the daily sessions. The IV saline injections were given manually through a hand-held syringe. The infusion pumps were disconnected for five rats whose catheters were

blocked during the last 2 days of the training phase or during extinction. These rats were given daily injections of saline (SC) before the start of the sessions. Extinction sessions continued for 5–10 days (one 1-h session/day) until the rats achieved the extinction criterion of <15 responses on the active lever.

Test 1: reinstatement

After extinction of nicotine-taking behavior, the effects of priming injections of nicotine (75, 150, 300 μg/kg, SC; and 30, 60 μg/kg, IV), or saline, on reinstatement of drug seeking were determined in separate daily sessions. Rats with patent catheters were tested after injections of both IV and SC priming drug injections, while rats with blocked catheters were tested after SC priming drug injections only. The order of drug doses and the route of administration was counterbalanced. During the tests for reinstatement, lever presses resulted in saline infusions for the eight rats with patent catheters. The infusion pumps were disconnected for five rats whose catheters were blocked. Priming injections were given just prior to the start of the test sessions. One rat was not tested because it did not reach the extinction criterion after ten sessions. The doses used for nicotine priming administered IV are based on the observations from previous work with opioid and stimulant drugs which indicate that the most effective doses for reinstatement of drug seeking are those that are similar to, or higher than, the self-administration unit dose (de Wit and Stewart 1981, 1983). The doses for nicotine priming administered SC are based on previous work on the sensitization of locomotor activity by nicotine (Corrigall et al. 1994). Also, so as not to confound the effect of priming injections of nicotine with spontaneous recovery (see below), rats were always given priming injections of saline on Monday, and if they responded on the active lever more than 15 times, extinction sessions were continued until the criterion of extinction was re-established. Finally, in order to determine whether repeated testing with nicotine alters extinguished drug seeking, the rats were given one more session of 60 min of exposure to the self-administration boxes, but without priming drug injections; this occurred at the end of the first set of tests for reinstatement. Lever press scores during this day were similar to those obtained after SC or IV saline injections (data not shown).

Test 2: reinstatement and spontaneous recovery

Rats were not exposed to the self-administration environment for 21 days. After this time, a number of the subjects had non-patent catheters. For this reason, in the second set of testing, the infusion pumps were disconnected and rats were only tested after SC injections. Initially the animals were tested for spontaneous recovery. During this test, rats were administered an injection of saline (SC), and placed in the self-administration boxes for 60 min. Subsequently, rats were given up to six more days of extinction sessions until they reached the extinction criterion of <15 responses on the active lever. Rats were given daily priming injections of saline (SC) during these sessions. The subjects were then given daily tests for reinstatement after exposure to SC priming injections of nicotine (150 and 300 μg/kg). The order of the doses was counterbalanced.

Experiment 2: reinstatement of food seeking

Drug-naive rats

Ten rats were trained to press a lever for 45-mg food pellets; the training conditions closely resembled the conditions of nicotine self-administration. The sessions were 60 min in duration and occurred 5 days per week for a 3-week period. Rats were fed 20 g of chow daily, and training started after a 24-h period of food deprivation. Lever presses for food reinforcement were initiated on an FR-1 schedule with a 15-s timeout period. In week 2, the response requirement was increased to FR-3 and in week 3, the response requirement was increased to FR-5. Responses on one of the levers (active lever) resulted in food pellets when the schedule requirements were met, while responses on the other lever (inactive lever) were recorded but were never reinforced with food. Subsequently, rats experienced six to eight daily extinction sessions in which lever presses did not result in food reinforcement. Prior to these sessions, the rats were given saline injections (SC). The extinction criterion used was 30 responses on the active lever. A higher extinction criterion than the one used in the nicotine self-administration study was chosen since the animals responded typically hundreds of times during the sessions for food. When the extinction criterion was reached, the rats were tested daily for reinstatement of food seeking after priming injections of nicotine (75, 150 and 300 μg/kg, SC) administered prior to the start of the sessions. After this dose-response determination, we also measured the effect of non-contingent exposure to food (one Noyes pellet was put in the food cup before the start of the session), and of injections of the D_2-like agonist, bromocriptine (Seeman and Van Tol 1994). The latter condition was tested in order to gain some insight into the reasons for the differential effect of nicotine on reinstatement of food seeking in nicotine-experienced and nicotine-naive rats. That is, nicotine reinstated food seeking in drug-experienced rats but not in drug-naive rats (see Results section). This observation might be related to the ability of nicotine to activate the mesolimbic DA system, involved in drug-seeking and motivated behavior (see Discussion section), more effectively in nicotine-treated than in nicotine-naive rats. Therefore, we tested whether activation of D_2-like receptors would reinstate food seeking. Bromocriptine methane sulfonate (RBI, Natick, Mass., USA; 4 and 8 mg/kg, IP; dose expressed as a salt) was injected 2 h before the tests for reinstatement of food seeking. Bromocriptine was dissolved in propylene glycol and a few drops of 70% ethanol.

Nicotine-experienced rats

Eight rats from experiment 1 were tested in the food-training operant chambers after the end of the first set of tests for reinstatement of nicotine seeking. On day 1, the rats responded for food on an FR-1 schedule of reinforcement (session duration of 60 min). On days 2 and 3, an FR-5 schedule of reinforcement was used. Subsequently rats were given five daily extinction sessions during which lever presses did not result in food reinforcement; on each of these sessions, a saline injection (SC) was administered before the session. The subjects were then given priming injections of nicotine (75, 150 and 300 μg/kg, SC). One rat was not tested because it did not meet the extinction criterion of 30 responses.

Results

Experiment 1: reinstatement and spontaneous recovery of nicotine seeking

In the last 3 days of training on the FR-5 schedule of reinforcement for nicotine self-administration (30 μg/kg per infusion), the rats obtained 12.5±0.9, 12.4±1.2 and 11.0±0.9 infusions in the 60-min sessions (mean±SEM). Unlike the situation for the self-administration of opioid and stimulant drugs, the rats did not show an "extinction burst" on day 1 of extinction when saline was substituted for nicotine (5.2±0.8 infusions in the 60-min session). These values are similar to the data reported in previous studies (Corrigall and Coen 1991; Donny et al. 1995).

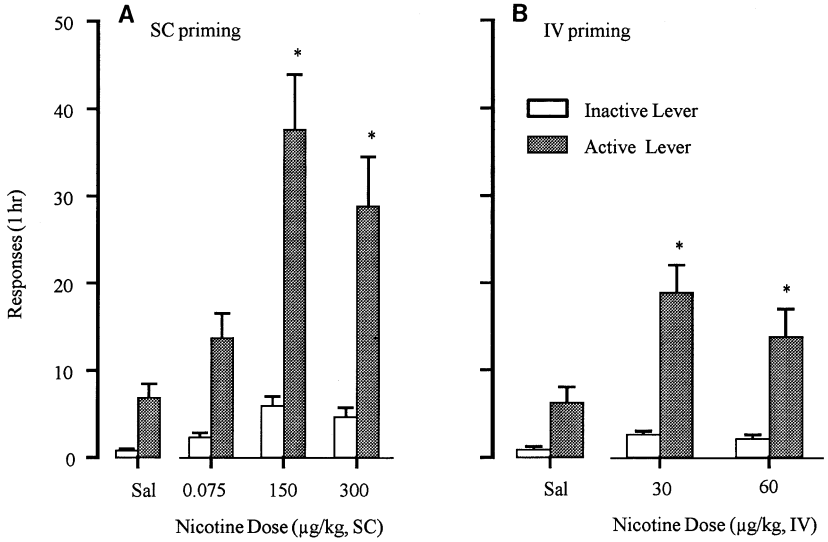

Fig. 2A, B Test 1: reinstatement of nicotine seeking. Mean (±SEM) number of presses on the previously active and inactive levers in the 60 min after **A** non-contingent SC saline and nicotine injections (n=12), and **B** non-contingent IV saline and nicotine injections (n=8). *Different from the saline priming conditions, P<0.05

Test 1: reinstatement

Figure 2 shows the mean number of responses on the active and inactive levers during the initial set of tests for reinstatement of nicotine seeking after exposure to non-contingent IV (n=8) and SC (n=12) priming injections of nicotine and saline. Nicotine reinstated drug seeking regardless of the route of administration. For the SC route of administration, a repeated-measures ANOVA, conducted on the data for responding on the active lever, revealed a significant effect of nicotine dose [F(3, 33)=12.6, P<0.01]. For the IV route, a repeated-measures ANOVA, conducted on the response data for the active lever, also revealed a significant effect of nicotine dose [F(2, 14)=6.7, P<0.01]. Post hoc differences between the nicotine doses and the saline priming condition are indicated in Fig. 2. The statistical analyses also revealed significant effects of nicotine dose for response scores for the inactive lever [a measure of nonspecific activity; F(3, 33)=12.2, P<0.01 and F(2, 14)=8.4, P<0.01 for the SC and the IV route of administration, respectively]. Therefore, difference scores (presses on the active lever minus presses on the inactive lever) were used in additional repeated measure ANOVAs. These analyses essentially replicated the statistical results obtained for lever presses on the active lever [F(3, 33)=12.5, P<0.01 and F(2, 14)=4.4, P<0.02 for the SC and the IV route of administration, respectively]. Finally, examination of shorter intervals (i.e., 20 min) within the 1-h session did not reveal different temporal patterns of reinstatement of drug seeking for either route of administration, or for any dose. In general, most responses occurred in the first 40 min of the test sessions.

Test 2: reinstatement and spontaneous recovery

Figure 3 shows the mean number of lever presses on the active and inactive levers during the second set of tests for reinstatement and spontaneous recovery (n=13).On

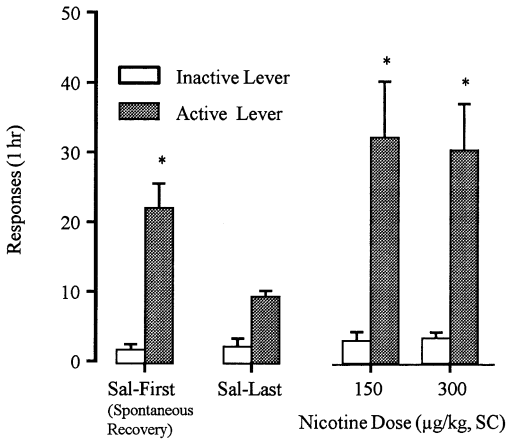

Fig. 3 Test 2: reinstatement and spontaneous recovery of nicotine seeking. Mean (±SEM) number of presses on the previously active and inactive levers in the 60 min after exposure to SC priming injections of saline 21 days after last exposure to the self-administration boxes (Sal-First, test of spontaneous recovery), after SC saline injections on the day in which the extinction criterion was met (*Sal-Last*), and after priming injections of nicotine given on the days following the day in which the extinction criterion was met (n=13). *Different from the baseline saline priming condition (Sal-Last), P<0.05

day 1 after the 3-week hiatus in exposure to the self-administration chambers, rats whose responding had been previously extinguished showed spontaneous recovery of responding on the active lever. Significant differences were observed between the lever press scores on the active lever after SC priming injections of saline in the first set of tests for reinstatement and the lever press scores during the "spontaneous recovery" day [F(1, 11)=10.7, P<0.01]. Furthermore, after the rats met the extinction criterion of 15 lever presses per hour, SC priming injections of nicotine retained their ability to reinstate drug seeking [F(2, 24)=5.7, P<0.01, for a nicotine dose]. Post hoc differences between the nicotine doses and the saline priming condition are indicated in Fig. 3. Nicotine did

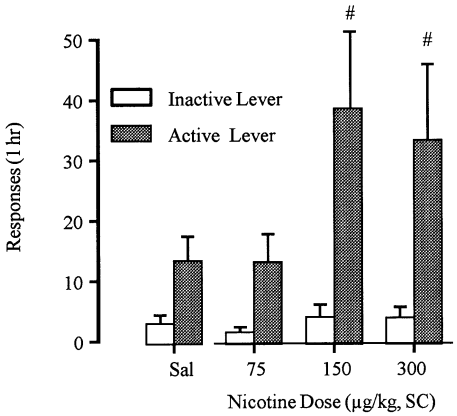

Fig. 4 Reinstatement of food seeking: nicotine experienced rats. Mean (±SEM) number of presses on the previously active and inactive levers in the 60 min after non-contingent SC saline and nicotine injections in nicotine-experienced rats (n=7). #Different from the saline priming condition, P<0.07

not alter lever presses on the inactive lever [F(2, 24)=0.38, NS].

Experiment 2: reinstatement of food seeking

Figure 4 shows the mean number of lever presses on the active and inactive levers after non-contingent priming injections of saline and nicotine in nicotine-experienced rats (n=7). Priming injections of nicotine reinstated food seeking in these rats [F(3, 18)=3.6, P<0.03 for the effect of a nicotine dose on lever press scores for the active lever]. Post hoc differences between the nicotine doses and the saline priming condition are indicated in Fig. 4. Nicotine did not alter lever presses on the inactive lever [F(3, 18)=1.1, NS]. Figure 5 shows the mean number of lever presses on the active and inactive levers after exposure to non-contingent priming injections of saline and nicotine, non-contingent priming injections of bromocriptine, and non-contingent exposure to food in drug-naive rats (n=10). Priming injections of nicotine had a variable, statistically non-significant effect on the reinstatement of food seeking in nicotine-naive rats [F(3, 27)=1.1, NS, for the effect of a nicotine dose on lever press scores of the active lever]. The D_2-like agonist, bromocriptine, in contrast, significantly reinstated food seeking. However, large individual differences were observed after injections of bromocriptine (the range of scores for the 4 and 8 mg/kg doses were 10–239 and 2–520 lever presses on the active lever, respectively). Therefore, the repeated-measures ANOVA, including the baseline saline priming condition and the two doses of bromocriptine, was conducted on logarithmic transformations of the scores. This analysis revealed a main effect of bromocriptine dose [F(2, 18)=3.9, P<0.05]. Post hoc differences between the bromocriptine doses and the saline priming condition are indicated in Fig. 5. As expected, non-contingent exposure to a 45-mg food pellet reinstated food seeking [F(1, 9)=14.1, P<0.01 for the comparison between the saline priming baseline condition and the food reinstatement condition]. Nicotine, bromocriptine and non-contingent exposure to food did not significantly alter lever presses on the inactive lever (see Fig. 5).

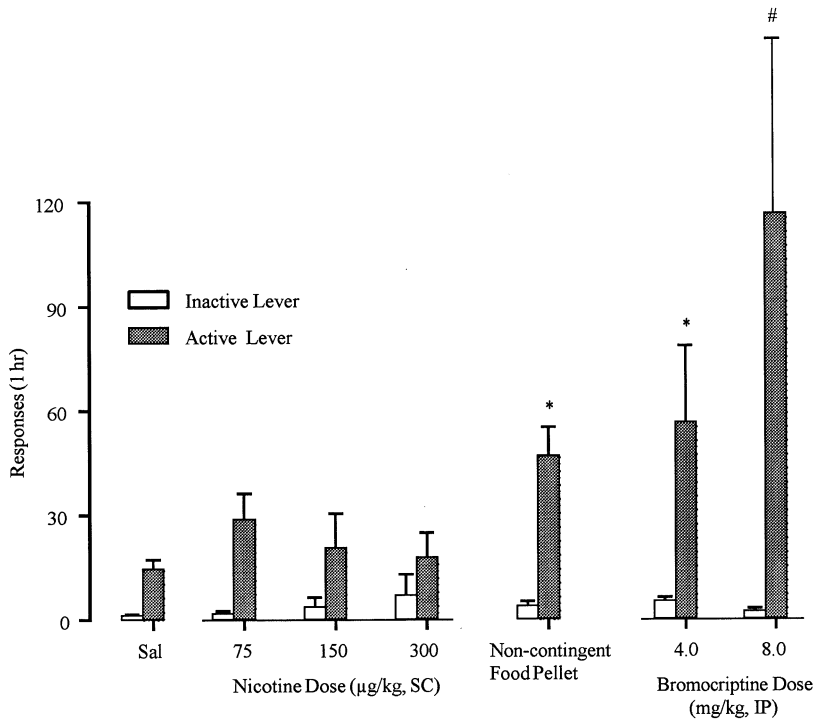

Fig. 5 Reinstatement of food seeking: nicotine-naive rats. Mean (±SEM) number of presses on the previously active and inactive levers in the 60 min after non-contingent saline, nicotine and bromocriptine injections, and non-contingent exposure to one 45-mg food pellet (n=10). *****Different from the saline priming condition, P<0.05. #Different from the saline priming condition, P=0.06

Discussion

Two main findings were obtained in experiment 1. First, acute re-exposure to nicotine reliably reinstated extinguished drug-taking behavior. This effect was independent of the route of administration and occurred after prolonged drug-free and extinction periods. Furthermore, the magnitude of the reinstatement effect, particularly with the SC route, was similar to that observed after priming injections of opioid and stimulant drugs after prolonged extinction and drug-free periods (Shaham and Stewart 1995; Erb et al. 1996; Shaham et al. 1996). Also consonant with the observations for opioid and stimulant drugs, the reinstatement effect of nicotine was observed at doses that are similar to, or higher than, the self-administration dose. These results are different from those obtained by Chiamulera et al. (1996), who reported reinstatement of nicotine seeking only at doses that were much lower than the self-administration dose. The reason for this discrepancy is not clear to us. It is also not entirely clear why nicotine reinstated drug seeking more effectively when it was administered via the SC route compared with the IV route. This observation may reflect the fact that higher doses of nicotine were administered via the SC route. We did not test higher doses of intravenous nicotine for fear of eliciting convulsions.

The second main finding in the present study is that the spontaneous recovery of responding, that is, the resumption of extinguished responding after the passage of time, occurred in nicotine-experienced rats. Furthermore, the effect was similar in magnitude to that of acute re-exposure to the drug. The magnitude of the spontaneous recovery of nicotine seeking is also similar to the spontaneous recovery of cocaine seeking after about 1 month without exposure to the self-administration chambers (Erb et al. 1996). As noted earlier, spontaneous recovery has been documented to occur with behaviors previously controlled by reinforcing events (Bouton and Swartzentruber 1991), but it has not been systematically studied in the context of relapse to drug use. Spontaneous recovery has obvious relevance to the understanding of relapse in tobacco users because many drug users resume drug-taking after prolonged abstinence periods.

An important question that cannot be answered from the present data is the nature of the neurochemical events involved in the reinstatement and spontaneous recovery of nicotine seeking. It is likely that the mesolimbic dopamine (DA) system, involved in the acute reinforcing effects of nicotine (Corrigall et al. 1992, 1994), as well as the reinstatement effect of opioid and stimulant drugs (Stewart 1984; Stewart and Vezina 1988), also mediates the reinstatement effect of nicotine. Nicotine, at doses comparable to those used in the present study, increases dopamine overflow in the nucleus accumbens (Di Chiara and Imperato 1988; Benwell and Balfour 1992; Nisell et al. 1994; Pontieri et al. 1996), a terminal region of the mesolimbic DA system implicated in the reinforcing (Koob and Bloom 1988; Wise 1996) and the reinstating (Stewart and Vezina 1988) effects of opioid and stimulant drugs.

At this time, however, it is difficult to speculate about the neurochemical events involved in spontaneous recovery of nicotine seeking. It is possible that environmental cues provoke drug seeking because they activate the neural substrates that mediate relapse after acute re-exposure to the drug (Stewart et al. 1984; Robinson and Berridge 1993). However, other alternatives must be considered. We have found that several pharmacological manipulations which block the reinstatement effect of heroin priming (i.e., the opioid antagonist naltrexone, the D_2-like DA antagonist raclopride, a maintenance dose of heroin) do not influence stress-induced reinstatement (Shaham and Stewart 1996; Shaham et al. 1996). McFarland and Ettenberg (1995), using a runway model of drug seeking, showed that the DA antagonist haloperidol attenuates the ability of acute re-exposure to heroin to provoke drug seeking. Haloperidol, however, has no effect on drug seeking provoked by exposure to stimuli that predict the availability of heroin. Finally, Wilson et al. (1995), using a conditioned fear procedure, reported that fornix lesions abolish the reinstatement effect of acute re-exposure to footshock, but have no effect on spontaneous recovery. Taken together, these observations raise the possibility that the neurochemical events involved in reinstatement and spontaneous recovery to nicotine seeking are not identical.

Another finding in this study is that nicotine reinstates food seeking in rats that previously self-administered the drug, but not in nicotine-naive rats. One possible explanation for this discrepancy lies in the similarity of the operant chambers for food and nicotine self-administration; perhaps the presence of nicotine in the body reinstated drug seeking, rather than food seeking, in a context similar to the drug environment. Alternatively, it is possible that nicotine has different effects on brain systems involved in reinstatement in drug-naive and in nicotine-experienced rats. Our data on the effect of bromocriptine on extinguished food seeking suggest that the activation of the DA system contributes to reinstatement of food seeking, as it does to the reinstatement of drug seeking (Stewart 1984; Stewart and Vezina, 1988; Wise et al. 1990; Self et al. 1996). Several reports suggest that nicotine is less effective in activating the mesolimbic DA system in drug-naive rats compared with nicotine-experienced rats. For example, it has been shown that nicotine increases locomotor activity (a behavior dependent on the functioning of the mesolimbic DA system (Wise and Bozarth 1987), after chronic, but not after acute, drug injections (Clarke and Kumar 1983; Corrigall et al. 1994). In addition, Reid et al. (1996) showed that nicotine injected SC is more effective in increasing DA utilization in the nucleus accumbens in nicotine-experienced rats than in nicotine-naive rats. Thus, to the extent that the mesolimbic DA system is involved in reinstatement of extinguished operant responding for non-drug reinforcers, nicotine may not be an effective stimulus in drug-naive rats.

Finally, there is still a debate about the degree to which nicotine addiction is a process similar to cocaine and heroin addiction (Henningfield and Heishman 1995). The present study demonstrates that the reinstatement effect of nicotine is similar to the reinstatement of opioid and stimulant drugs. Our data also demonstrate that, as with other drug and non-drug reinforcers, spontaneous recovery occurs after extinction of nicotine seeking. These data provide further support for the notion that similar mechanisms mediate the compulsive use of stimulant and opioid drugs and the compulsive use of nicotine.

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References

Benwell MEM, Balfour DJK (1992) The effect of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol 105: 849–856

Bouton ME, Swartzentruber D (1991) Sources of relapse after extinction in Pavlovian and Instrumental learning. Clin Psychol Rev 11: 123–140

Bozarth MA, Pudiak CM (1996) Intravenous nicotine self-administration in laboratory animals: chasing the enigma. Soc Neurosci Abstr 22: 163

Carmody TP (1992) Preventing relapse in the treatment of nicotine addiction: current issues and future directions. J Psychoactive Drugs 24: 131–158

Carroll ME, Comer SD (1996) Animal models of relapse. Exp Clin Psychopharmacol 4: 11–18

Catania CA (1992) Learning, 3rd edn. Prentice-Hall, Englewood, Cliffs.

Chiamulera C, Borgo C, Falchetto S, Valerio E, Tessari M (1996) Nicotine reinstatement of nicotine self-administration after long-term extinction. Psychopharmacology 127: 102–107

Chornock WM, Stitzer ML, Gross J, Leischow S (1992) Experimental model of smoking re-exposure: effects on relapse. Psychopharmacology 108: 495–500

Clarke PBS, Kumar R (1983) The effects of nicotine on locomotor activity in non-tolerant and tolerant rats. Br J Pharmacol 78: 329–337

Corrigall WA, Coen KM (1989) Nicotine maintains robust self-administration in rats on a limited access schedule. Psychopharmacology 99: 473–478

Corrigall WA, Coen KM (1991) Selective dopamine antagonists reduce nicotine self-administration. Psychopharmacology 104: 171–176

Corrigall WA, Franklin KBJ, Coen KM, Clarke PBS (1992) The mesolimbic dopamine system is implicated in the reinforcing effects of nicotine. Psychopharmacology 107: 285–289

Corrigall WA, Coen KM, Adamson KL (1994) Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res 653: 278–284

de Wit H (1996) Priming effects with drugs and other reinforcers. Exp Clin Psychopharmacol 4: 5–10

de Wit H, Stewart J (1981) Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology 75: 134–143

de Wit H, Stewart J (1983) Drug reinstatement of heroin-reinforced responding in the rat. Psychopharmacology 79: 29–31

Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine transmission concentration in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 85: 5274–5278

Donny EC, Caggiula AR, Knopf S, Brown C (1995) Nicotine self-administration in rats. Psychopharmacology 122: 390–394

Dworkin SI, Varna SL, Broadbent J, Robinson JH (1993) Comparing the reinforcing effects of nicotine, caffeine, methylphenildate and cocaine. Med Chem Res 2: 593–602

Epping-Jordan MP, Markou A, Koob GF (1996) Intravenous self-administration of nicotine in rats. Behav Pharmacol 7[suppl]: 35

Erb S, Shaham Y, Stewart J (1996) Stress reinstates cocaine-seeking behavior after prolonged extinction and drug-free periods. Psychopharmacology 128: 408–412

Gerber GJ, Stretch R (1975) Drug-induced reinstatement of extinguished self-administration behavior in monkeys. Pharmacol Biochem Behav 3: 1055–1061

Henningfield JE, Heishman SJ (1995) The addictive role of nicotine in tobacco use. Psychopharmacology 117: 11–13

Hunt WA, Barnett LW, Branch LG (1971) Relapse rates in addiction programs. J Clin Psychol 27: 455–456

Jaffe JH, Cascell NG, Kumor KM, Sherer MA (1989) Cocaine-induced cocaine craving. Psychopharmacology 97: 59–64

Koob GF, Bloom FE (1988) Cellular and molecular mechanisms of drug dependence. Science 242: 715–723

Ludwig AM, Wikler A, Stark LH (1974) The first drink. Psychobiological aspects of craving. Arch Gen Psychiatry 30: 539–547

Markou A, Weiss F, Gold LH, Caine B, Schulteis G, Koob GF (1993) Animal models of drug craving. Psychopharmacology 112: 163–182

McFarland K, Ettenberg A (1995) Haloperidol differentially affects reinforcement and motivational processes in rats running an alley for intravenous heroin. Psychopharmacology 122: 346–350

Meyer RE, Mirin SM (1979) The heroin stimulus: implications for a theory of addiction. Plenum Press, New York

Nisell M, Nomikos GG, Svensson TH (1994) Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotine receptors in the ventral tegmental area. Synapse 16: 36–44

Pontieri FW, Tanda G, Orzi F, Di Chiara G (1996) Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 382: 255–257

Reid MS, Ho LB, Berger PS (1996) Effects of environmental conditioning on the development of nicotine sensitization: behavioral and neurochemical analysis. Psychopharmacology 126: 301–310

Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 18: 247–291

Seeman P, Van Tol HM (1994) Dopamine receptor pharmacology. Trends Pharmacol Sci 15: 264–270

Self DW, Barnhart WJ, Lehman DA, Nestler EJ (1996) Opposite modulation of cocaine-seeking behavior by D_1- and D_2-like dopamine receptor agonists. Science 271: 1586–1589

Shaham Y, Stewart J (1995) Stress reinstates heroin self-administration behavior in drug-free animals: an effect mimicking heroin, not withdrawal. Psychopharmacology 119: 334–341

Shaham Y, Stewart J (1996) Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. Psychopharmacology 125: 385–391

Shaham Y, Rodaros M, Stewart J (1994) Reinstatement of heroin-reinforced behavior following a long-term extinction: implications for the treatment of relapse to drug-taking. Behav Pharmacol 5: 360–364

Shaham Y, Rajabi H, Stewart J (1996) Relapse to heroin-seeking under opioid maintenance: the effects of opioid withdrawal, heroin priming and stress. J Neurosci 16: 1957–1963

Shoaib MS, Swanner LS, Prada J, Yasar S, Goldberg SR (1996) Caffeine potentiates both acquisition and maintenance of intravenous nicotine self-administration. Behav Pharmacol 7[suppl]: 103

Shoaib M, Schindler CW, Goldberg SR (1997) Nicotine self-administration in rats: strain and nicotine pre-exposure effects on acquisition. Psychopharmacology 129: 35–43

Stewart J (1984) Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of

morphine in the ventral tegmental area. Pharmacol Biochem Behav 20: 917–923

Stewart J, de Wit H (1987) Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In: Bozarth MA (ed) Methods of assessing the reinforcing properties of abused drugs. Springer, New York, pp 211–227

Stewart J, Vezina P (1988) A comparison of the effects of intra-accumbens injections of amphetamine and morphine on reinstatement of heroin intravenous self-administration behavior. Brain Res 457: 287–294

Stewart J, de Wit H, Eikelboom R (1984) Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychol Rev 91: 251–268

Stretch R, Gerber GJ, Wood SM (1971) Factors affecting behavior maintained by response-contingent intravenous infusions of amphetamine in squirrel monkeys. Can J Physiol Pharmacol 49: 581–589

Tessari M, Valerio E, Chiamulera C, Beardsley PM (1995) Nicotine reinforcement in rats with histories of cocaine self-administration. Psychopharmacology 121: 282–283

USDHHS (1988) The health consequences of smoking: nicotine addiction. A report of the Surgeon General. US Department of Health and Human Services, Rockville, Md.

Wilson A, Brooks DC, Bouton ME (1995) The role of the rat hippocampal system in several effects of context in extinction. Behav Neurosci 109: 828–836

Wise RA (1996) Neurobiology of addiction. Curr Opin Neurobiol 6: 243–251

Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psychol Rev 94: 469–492

Wise RA, Murray A, Bozarth MA (1990) Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. Psychopharmacology 100: 355–360