Pergamon

Pharmacology Biochemistry and Behavior, Vol. 50, No. 1, pp. 71-75, 1995

0091-3057/95 $9.50 + .00

0091-3057(94)00256-8

Stimulus Control of Addictive Behavior: Persistence in the Presence and Absence of a Drug

JOHN L. FALK[1] AND CHYAN E. LAU

Department of Psychology, Rutgers University, New Brunswick, NJ 08903

Received 16 June 1994

FALK, J. L. AND C. E. LAU. *Stimulus control of addictive behavior: Persistence in the presence and absence of a drug.* PHARMACOL BIOCHEM BEHAV **50**(1) 71-75, 1995.—Rats were exposed daily to a food schedule-induced polydipsia condition, in which water and 0.16 mg/ml cocaine solution were available concurrently, with the cocaine solution indicated by a discriminative stimulus (S^D) light. The cocaine solution was preferred, and the preference was maintained when the S^D was gradually eliminated by fading its intensity. For a second group, if cocaine concentration was the stimulus gradually eliminated, preference for the resulting solution (water) indicated by the S^D was stably maintained. For two additional groups, if either the light S^D or the cocaine stimulus was removed abruptly rather than gradually, few animals retained preferences. These studies reveal the importance of establishing strong stimulus control for the initiation and persistence of drug abuse behavior.

Drug self-administration Cocaine abuse Stimulus control Schedule-induced polydipsia

RESEARCH with nonhuman primates and rats given opportunities to self-administer drugs intravenously (IV) has demonstrated the abuse potential of agents from several pharmacologic classes (3,17,28,31). There is concordance between drugs that produce high and persistent self-injection rates in animals, and those possessing notable abuse liabilities in humans (13). However, an apparent discontinuity exists between the virtual certainty with which animals acquire strong and persistent IV drug taking, and the comparative resistance to addictive use most humans display, even after several episodes of self-administering a drug with high abuse potential. For example, of those individuals experimenting with cocaine, a drug with a clear potential for abuse, a relatively small proportion proceed to high-frequency use (14). Furthermore, for drugs with abuse liability that are taken over a long period by prescription, iatrogenic addiction and dependence is a comparatively rare event (23). Once acquired, however, drug abuse in humans can persist even when the available active agent has been greatly diluted. For example, the modal amount of heroin in samples obtained from street purchases during the 1970s was only 0.5% (18). In contrast, the self-injection behavior of animals remains sensitive to changes in the IV unit dose and its rate of delivery, with self-injection quickly decreasing to low levels upon the substitution of saline for drug solution (1,15).

Animals exposed to the usual experimental arrangement require no facilitating factors to initiate long-term IV drug self-injection because a brief episode of responding results in an immediate pharmacologic effect. Although drugs can compromise behavioral functioning, this does not limit drug taking, because impaired behavior results in little or no negative consequence in a protective laboratory environment, nor is drug taking by animals constrained by social disapproval. Under such conditions, contingent pharmacologic effects alone are sufficient to initiate and maintain IV self-injection of a wide range of drugs (31).

In situations in which humans are exposed, factors in addition to pharmacologic effects may be crucial for facilitating both the acquisition and maintenance of excessive drug taking (14,29,30). Pharmacologic consequences occur only after drug-seeking behavior has led to drug taking, imposing a delay between the initiation of behavior relevant to acquiring a drug and the consequent pharmacologic effects. In the present experiments, this delay of effect was accomplished by allowing

[1] Requests for reprints should be addressed to John L. Falk, Department of Psychology—Busch, Rutgers University, New Brunswick, NJ 08903. E-mail: JFALK@ZODIAC.RUTGERS.EDU

animals to ingest a drug solution orally, rather than by self-injection. In addition, situations within which humans develop their drug seeking have embedded within them stimuli that begin to evoke considerable drug-seeking behavior resulting from their past association with ultimate drug availability (2,4,16). Thus, exteroceptive stimuli guide and facilitate drug seeking under conditions in which the ensuing pharmacologic effects may be delayed or minimal. One aim of the present experiments was to evaluate the relative importance of stimulus control and pharmacologic consequences in determining the choice between a drug solution and its vehicle.

Chronic drug abuse in humans typically develops out of an antecedent context that gives rise to a range of disturbed and excessive behaviors. Drug abuse is only one feature of this broader picture of behavioral difficulties (21). Analogously, previous research exposing food-deprived animals to a context of intermittent food pellet delivery found they often develop concurrent, excessive behaviors (5,6). Although several noningestive behavioral excesses have been explored (e.g., aggression and hyperactivity), an ingestive alternative, schedule-induced drug intake, has proved useful in evoking chronic, excessive drug-solution drinking, as well as facilitating weak IV self-injection behavior (7). In the present experiment, schedule-induced polydipsia was used to provoke chronic and excessive fluid intake upon which drug overindulgence could develop.

When rats were allowed a history of preferring an ethanol solution to concurrently available water under a schedule-induced polydipsia condition, drug preference was maintained when the solution was gradually changed from ethanol to cocaine (9). (In a previous study, which did not use an initial history phase of ethanol preference, rats did not prefer cocaine solution to water [12].) The daily left–right position at which the drug solution was available varied, and its location was indicated by the adjacent presence of a discriminative stimulus (S^D) light. The choice and excessive intake of cocaine was found to be a function of the associative history of the S^D with the ethanol solution. After association of the S^D with a series of drug solutions, animals continued to choose and ingest the fluid indicated by the S^D, even when that fluid was simply an alternative source of water.

The efficacy and durability that the S^D acquired in determining the polydipsic choice suggested an important function for environmental S^D in the development and maintenance of drug abuse. The present experiments were designed to ascertain several features of the S^D control of excessive intakes: a) the durability of the S^D control of intake when drug content was discontinued—that is, the susceptibility of S^D control to extinction; b) the possibility that gustatory properties of a drug solution could serve an S^D function; and c) determination of whether a gradual transformation of one S^D controlling condition into another is a necessary feature in effecting a transfer in the environmental control of drug seeking and drug taking, or whether an abrupt S^D change also would permit a transfer of control.

METHOD

Animals

Animals were 32 adult, albino, male rats of the Holtzman strain with a mean initial body weight of 385 g (range 380–408). They were housed individually in a temperature-regulated room with a 12-h light–dark cycle (lights on at 0700 h). They were maintained at 80% of their adult free- feeding body weights by limiting daily food rations over a 2-week period before the beginning of the experiment.

Procedure

Animals were divided into four groups (n = 8 each). They were transferred daily to individual Plexiglas chambers (26.5 × 26.5 × 20.7 cm) and exposed to a fixed-time (FT), 1-min food delivery schedule (FT 1 min) for 3-h sessions, with one or two sources of fluid available. The FT 1-min food schedule automatically delivered a 45-mg food pellet (BioServ, Frenchtown, NJ) once per minute, accompanied by an audible click. Food supplements required to maintain animals at 80% were given immediately after daily sessions in the individual home cages, where tap water was freely available. Experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publ. No. 85-23, revised 1985).

For 3–4 weeks, a single fluid, 2.5% (v/v) ethanol, was available during the session, which was was presented at a position to the left or right of the center position on one panel of the session chamber. This panel was opposite the food delivery panel. Session fluids were available from stainless-steel drinking spouts attached to Nalgene graduated cylinders. The center-to-center distance between spout positions was 7.5 cm. For the two groups exposed to the fading conditions (group conditions are subsequently described), the position of a drug solution was alternated daily, except as noted for the terminal condition in Fig. 1, for which drug position was quasirandom. For the two groups exposed to the abrupt-change conditions, the daily position of a drug solution was always quasirandom. Both positioning procedures proved adequate to control for side preference. Drug solution position always was indicated by illuminating an S^D light (0.65 candlepower) that transilluminated a beveled Plexiglas block (3.8 × 3.8 cm; Med Associates, ENV-227) next to the drinking spout. Two fluids were made available during sessions for the next 2 weeks, 2.5% ethanol and water, with the same drug positioning and S^D procedure remaining in effect.

After the establishment of chronic ethanol polydipsia and ethanol preference, the drug solution was altered. Ethanol content was gradually reduced to zero, whereas its cocaine HCl concentration was increased in two steps to 0.16 mg/ml. First, 0.08 mg/ml cocaine HCl was added to the 2.5% ethanol solution (two sessions), and then the ethanol content was reduced to 2.0% (two sessions). Next, the following concentration combinations were presented for four to six sessions each: Cocaine content remained constant at 0.16 mg/ml, whereas the ethanol concentration of the solution was reduced progressively to 2.0, 1.5, 1.0, 0.5, and 0.25%. Ethanol was then reduced to zero, and 0.16 mg/ml cocaine was presented for 16 sessions. Water remained the alternative fluid available.

The groups were then given different treatments, although all continued to receive daily FT 1-min, schedule-induced polydipsia sessions. For the S^D-fade group, the same fluid choices were continued, but the intensity of the S^D light associated with cocaine was gradually reduced (10-turn potentiometer fader; Med Associates, ENV-226) over a 4-week period from full intensity (fader setting = 10) to off (fader setting = 0), and remained off for an additional 4 weeks. The fading sequence for the S^D settings was two sessions each at 9.2 and 8.8, and four sessions each at 8.4, 8.0, 7.5, 7.0, 6.5, and 3.0, with the left–right drug alternating sequence maintained for 22 sessions at setting 0, and a quasirandom sequence maintained for eight sessions. For the cocaine-fade group, the S^D

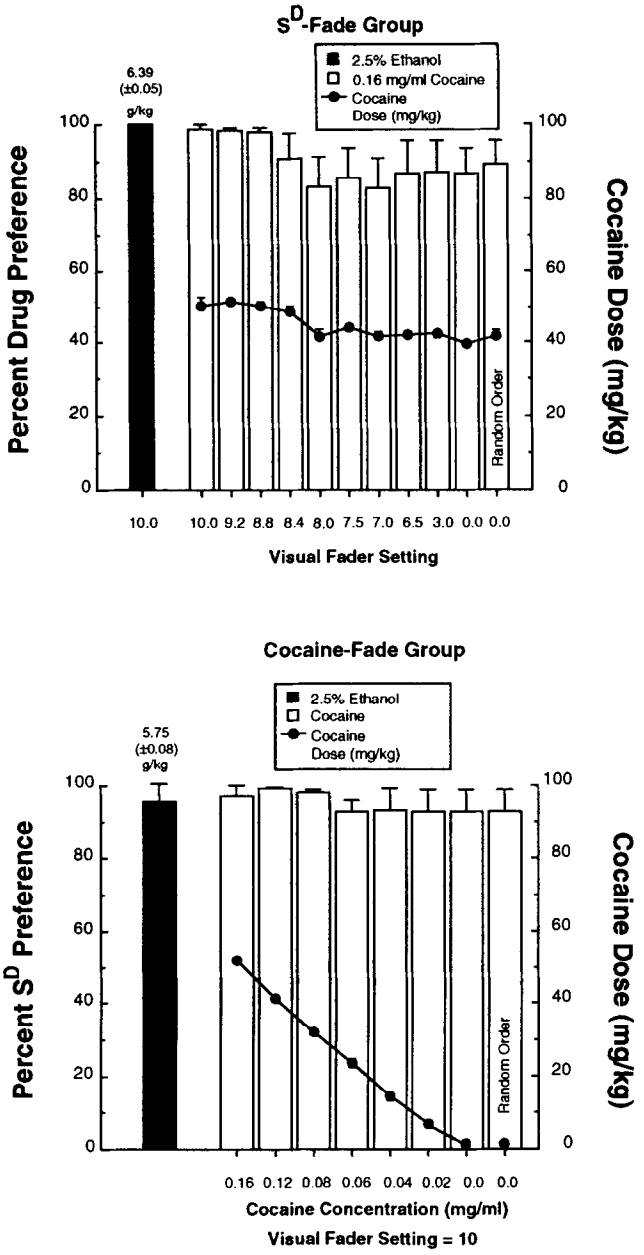

FIG. 1. Mean (SE) preference for oral cocaine solution as its discriminative stimulus light (S^D) was gradually decreased in intensity over 4 weeks from 10 to 0 (top), and preference for S^D-indicated solution as its cocaine concentration was gradually decreased over 4 weeks from 0.16 to 0 mg/ml (bottom). The last two bars (right, top and bottom) represent an additional 4 weeks for which the terminal condition was maintained. Daily session length = 3 h. n = 8 for each group. Concurrent alternative fluid offered was always water. (Visual fader settings are values on linear 10-turn potentiometer.)

light remained at full intensity, but the cocaine concentration was gradually reduced over a 4-week period from 0.16 to 0 mg/ml, and remained at zero for an additional 4 weeks. The fading sequence for cocaine was six sessions each at 0.12, 0.08, 0.06, 0.04, and 0.02 mg/ml, with the left-right S^D alternating sequence maintained for 20 sessions at 0 mg/ml, and a quasirandom sequence maintained for eight sessions.

RESULTS

The FT 1-min schedule induced a concurrent polydipsia during each session. In Figs. 1 and 2, the leftmost bar for each of the four groups shows that 2.5% ethanol was preferred to water almost exclusively when both were available concurrently. The mean (SE) session ethanol intake for each group is shown above each of these filled bars. After ethanol had been faded out, the second bar from the left for all groups shows the result for the 16-session period for which 0.16 mg/ml

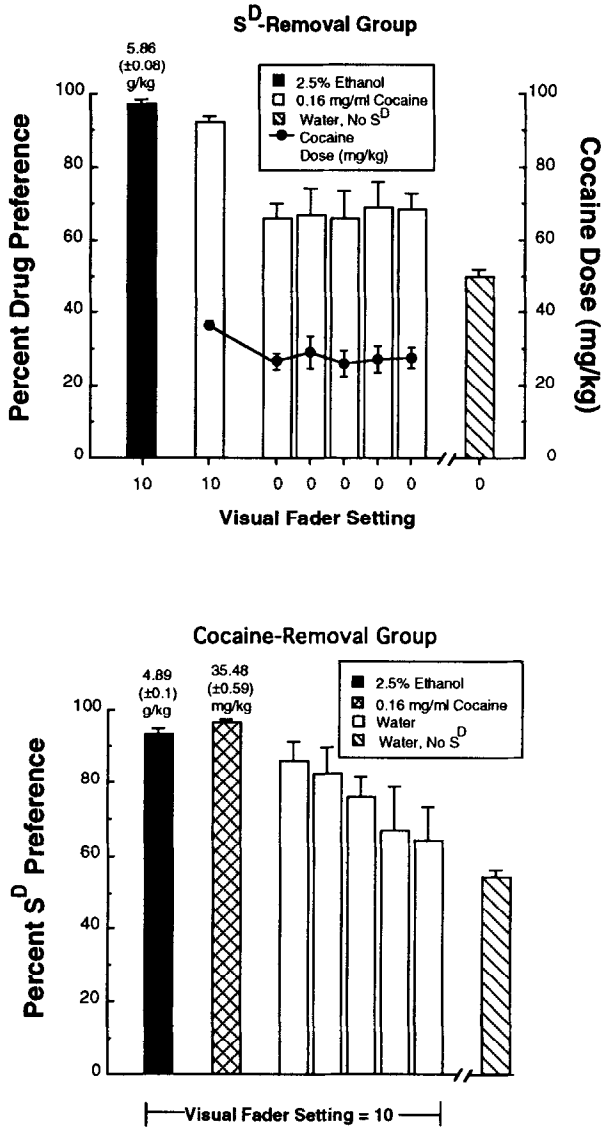

FIG. 2. Mean (SE) preference for oral cocaine solution when its discriminative stimulus light (S^D) was abruptly decreased in intensity from 10 to 0, with the middle five-bar block composed of five consecutive, six-session means (top); preference for S^D-indicated solution as its cocaine concentration was abruptly decreased from 0.16 mg/ml to water, with the middle five-bar block composed of five consecutive, six-session means (bottom). In both top and bottom, the rightmost bar shows the final control condition offering water concurrently at both positions without the S^D. Daily session length = 3 h. n = 8 for each group.

cocaine solution and water were concurrently available: The cocaine solution was preferred to water almost exclusively. The result of fading the light S^D is shown in Fig. 1 (top). Most of the animals in the S^D-fade group continued to show a strong preference for cocaine solution during S^D fading, and the preference remained high for the additional 4-week exposure period after the completion of S^D fading. One animal developed a position preference at and beyond fader setting 8.0, and drank whichever fluid was present in the righthand position. This is reflected in the slightly lower group cocaine preferences in Fig. 1 (top) at and beyond fader setting 8.0.

The cocaine-fade group (Fig. 1, bottom) continued to prefer the cocaine solution (proximate to the daily position of the S^D light) during solution concentration fading, and preference for the S^D-proximate fluid remained at its high level for the additional 4-week exposure period after the cocaine concentration had been reduced to zero. Neither group showed evidence of extinction of its preference during this final 4-week exposure period. (Preference extinction usually manifests as a preference for a particular position [left or right], so that whichever fluid is present at the preferred location is ingested, yielding a 50% preference value for both fluids.) Furthermore, the polydipsic intake levels of neither group decreased. In Fig. 2 (top), the center block of five bars indicates the preference for cocaine solution in successive, six-session blocks after the abrupt removal of the S^D for the S^D-removal group. The established cocaine preference (second bar) immediately fell precipitously, and the numbers of animals retaining $\geq$ 80% preference for the cocaine solution across the five blocks were two, three, three, three, and three of eight. As a final 10-day control condition, the S^D remained off, and both fluids offered were water. All animals in the group showed a preference for the water offered in the righthand position (Fig. 2, top, rightmost bar).

Upon cocaine removal (Fig. 2, bottom, 5-bar block) for the cocaine-removal group, preference for the S^D-proximate water source fell gradually, and the numbers of animals retaining $\geq$ 80% preference for the S^D-proximate fluid source across the five blocks were six, four, five, three, and two of eight. As a final 10-day control condition, the S^D was removed, and all animals showed a preference for the water offered in the righthand position (Fig. 2, bottom, rightmost bar).

DISCUSSION

The preference for ethanol solution to water for all groups confirmed previous results using low ethanol concentrations under schedule-induction conditions (22,25). This preference also occurred when the fluids were available under concurrent FR 6 schedules and food was available on a fixed-interval, 1-min schedule (9). Likewise, in the latter experiment, fading out ethanol from the same cocaine solution resulted in a preference for cocaine solution to water. The milligram per kilogram intakes of cocaine shown in the second bar for each group (Figs. 1 and 2) were similar and agree with the values observed in our previous research when this concentration was presented without a concurrent water alternative (11,26,27). Previous studies (10,24,26) have also shown that the schedule-induced intake of 0.16 mg/ml cocaine solution produced rat serum cocaine levels comparable to levels observed in humans chewing coca leaves.

The S^D-fade results demonstrated that a stable, chronic preference for cocaine solution to water was maintained in the absence of the visual S^D when the SD was faded gradually. The cocaine-fade results revealed that a stable, long-term choice of a water source was maintained when the water was presented proximate to the S^D light that had indicated cocaine, provided that the cocaine content was gradually faded to become water. In this operant study (9), in which a preference for cocaine solution to water was instituted by similar means (fading in cocaine while fading out ethanol, with S^D present), either abrupt S^D removal or abrupt S^D reversal (S^D relocated to be adjacent to water) resulted in the immediate loss of preference for cocaine solution. This result suggested that the retention of the preferences shown in Fig. 1 was critically dependent on gradual fading of whichever stimulus (visual or gustatory S^D) was associated with the unaltered stimulus that remained to control preference behavior. To confirm this conjecture, the same procedures were used with the groups shown in Fig. 2, except that when they were manipulated, the stimuli were changed abruptly (removed), rather than faded.

Figure 2 shows that abrupt removal of either the S^D or the cocaine content led to a loss of preference behavior for the majority of animals in the respective groups. This loss was immediate for the S^D-removal group, but developed more gradually for the cocaine-removal group. It is interesting that removal of the exteroceptive S^D effected a more rapid change in preference behavior than did the removal of cocaine content. Thus, rapid removal of salient S^Ds from a drug abuse context in which this is feasible may be a more effective therapeutic device than attempting to extinguish the S^Ds by presenting them in the absence of the drug. Insofar as both sorts of abrupt removal ultimately resulted in a loss of preference behavior for the majority of animals in both groups, it indicates that neither stimulus alone was sufficient for maintaining preference when its supporting counterpart was summarily discontinued. Both were important factors sustaining the continuing preference for cocaine solution. Clearly, one or the other was dispensible when faded, in contrast to its abrupt removal. But the difference between the result of fading and abrupt removal is not absolute; a few animals in each of the abrupt-removal groups did maintain their preferences.

Although these experiments demonstrated that, under an S^D condition indicating drug location, a preference for cocaine solution to water could be substituted for a previous preference for ethanol to water, the gradual fading of either the S^D intensity to zero or the cocaine concentration to zero left intact a strong preference for the unchanged stimulus condition: either cocaine solution or the water associated with the S^D. The strong and stable preference, as well as the persistent, excessive level of intake in both cases, indicates that current maintenance of addictive behavior may be attributable as much to the S^D determination of self-administration behavior as it is to past or present pharmacologic consequences (8). In both cases, the stimulus that remained unchanged after the other was gradually faded came to serve strong and equivalent S^D functions with respect to ingestive preference. Whether the S^D-fade group, which continued to prefer cocaine solution, also continued this preference as a result of a concurrent reinforcing effect of cocaine cannot be derived from these experiments. The previous demonstration of place-preference conditioning resulting from the schedule-induced intake of a 0.16 mg/ml cocaine solution is consistent with such a concurrent-reinforcement interpretation (24).

Individuals within the groups for which the manipulated stimulus was abruptly changed were much less likely to come under the enduring S^D control of the unchanged stimulus. The combined abrupt-removal conditions for these groups may be analogous to conditions faced by human drug abusers for whom an abrupt discontinuation of the drug, together with a

change in environmental S^Ds, leads to a dramatic and enduring decrease in drug addiction. This phenomenon was documented by the classic study of the rapid, unassisted recovery from heroin addiction by the great majority of dependent Vietnam veterans upon their return to the United States (20). The current interpretation of these results is that they reflect not the outcome of an unusual overseas situation, but rather the normal course of heroin addiction for an unselected subject population—that is, not one studied because they have come to treatment (19).

ACKNOWLEDGEMENTS

This research was supported by Grant R01 DA05305 from the National Institute on Drug Abuse and by Research Scientist Award K05 DA00142 (to J.L.F.). Cocaine HCl was obtained from the National Institute on Drug Abuse, Rockville, Maryland.

REFERENCES

1. Balster, R. L.; Schuster, C. R. Fixed-interval schedule of cocaine reinforcment: Effect of dose and infusion duration J. Exp. Anal. Behav. 20:119–129; 1973.
2. Childress, A. R.; McLellan, A. T.; Ehrman, R.; O'Brien, C. P. Classically conditioned responses in opioid and cocaine dependence: A role in relapse? In: Ray, B. A., ed. Learning factors in substance abuse. (NIDA Res. Mongr. No. 84) Washington, DC: U.S. Govt. Printing Office; 1988:25–43.
3. Deneau, G.; Yanagita, T.; Seevers, M. H. Self-administration of psychoactive substances by the monkey. Psychopharmacologia 16:30–48; 1969.
4. Ehrman, R. N.; Robbins, S. J.; Childress, A. R.; O'Brien, C. P. Conditioned responses to cocaine-related stimuli in cocaine abuse patients. Psychopharmacology 107:523; 1992.
5. Falk, J. L. Production of polydipsia in normal rats by an intermittent food schedule. Science 133:195–196; 1961.
6. Falk, J. L. The environmental generation of excessive behavior. In: Mulé, S. J., ed. Behavior in excess. New York: Free Press; 1981:313–387.
7. Falk, J. L. Schedule-induced drug self-administration. In: van Haaren, F., ed. Methods in behavioral pharmacology. Amsterdam: Elsevier; 1993:301–328.
8. Falk, J. L. The discriminative stimulus and its reputation: Role in the instigation of drug abuse. Exp. Clin. Psychopharmacol. 1:43–52; 1994.
9. Falk, J. L.; Lau, C. E. Oral cocaine as a reinforcer: Acquisition conditions and importance of stimulus control. Behav. Pharmacol. 4:597–609; 1993.
10. Falk, J. L.; Ma, F.; Lau, C. E. Chronic oral cocaine self-administration: Pharmacokinetics and effects on spontaneous and discriminative motor functions. J. Pharmacol. Exp. Ther. 257:457–465; 1991.
11. Falk, J. L.; Tang, M. Schedule induction of drug intake: Differential responsiveness to agents with abuse potential. J. Pharmacol. Exp. Ther. 249:143–148; 1989.
12. Falk, J. L.; Vigorito, M.; Tang, M.; Lau, C. E. Schedule-induced cocaine drinking: Choice between cocaine and vehicle. Pharmacol. Biochem. Behav. 35:187–193; 1990.
13. Griffiths, R. R.; Bigelow, G. E.; Henningfield, J. E. Similarities in animal and human drug-taking behavior. In: Mello, N. K., ed. Advances in substance abuse, vol. 1. Greenwich, CN: JAI Press; 1980:1–90.
14. Kandel, D. B.; Murphy, D.; Karus, D. Cocaine use in young adulthood: Patterns of use and psychosocial correlates. In: Kozel, N. J.; Adams, E. H., eds. Cocaine use in America: Epidemiologic and clinical perspectives. (NIDA Res. Monogr. No. 61) Washington, DC: U.S. Govt. Printing Office; 1985:76–110.
15. Kato, S.; Wakasa, Y.; Yanagita, T. Relationship between minimum reinforcing doses and injection speed in cocaine and pentobarbital self-administration in crab-eating monkeys. Pharmacol. Biochem. Behav. 28:407–410; 1987.
16. O'Brien, C. P.; Childress, A. R.; McLellan, A. T.; Ehrman, R.; Ternes, J. W. Types of conditioning found in drug-dependent humans. In: Ray, B. A., ed. Learning factors in substance abuse. (NIDA Res. Mongr. No. 84) Washington, DC: U.S. Govt. Printing Office; 1988:44–61.
17. Pickens, R.; Thompson, T. Cocaine-reinforced behavior in rats: Effects of reinforcement magnitude and fixed-ratio size. J. Pharmacol. Exp. Ther. 161:122–129; 1968.
18. Primm, B. J.; Bath, P. E. Pseudoheroinism. Int. J. Addict. 8: 231–242; 1973.
19. Robbins, L. N. Vietnam veterans' rapid recovery from heroin addiction: A fluke or normal expectation? Addiction 88:1041–1054; 1993.
20. Robins, L. N.; Helzer, J. E.; Davis, D. H. Narcotic use in Southeast Asia and afterward: An interview study of 898 Vietnam returnees. Arch. Gen. Psychiatry 32:955–961; 1975.
21. Robins, L. N.; Przybeck, T. R. Age of onset of drug use as a factor in drug and other disorders. In: Jones, C. L.; Battjes, R. J., eds. Etiology of drug abuse: Implications for prevention. (NIDA Res. Monogr. No. 56) Washington, DC: U.S. Govt. Printing Office; 1985:178–192.
22. Samson, H. H.; Falk, J. L. Alteration of fluid preference in ethanol-dependent animals. J. Pharmacol. Exp. Ther. 190:365–376; 1974.
23. Schuster, C. R. Testing and abuse liability of drugs in humans. In: Fischman, M. W.; Mello, N. K., eds. Testing for abuse liability of drugs in humans. (NIDA Res. Mongr. No. 92) Washington, DC: U.S. Govt. Printing Office; 1989:1–6.
24. Seidman, M. H.; Lau, C. E.; Chen, R.; Falk, J. L. Orally self-administered cocaine: Reinforcing efficacy by the place preference method. Pharmacol. Biochem. Behav. 43: 235–241; 1992.
25. Tang, M.; Falk, J. L. Ethanol dependence as a determinant of fluid preference. Pharmacol. Biochem. Behav. 7:471–474; 1977.
26. Tang, M.; Falk, J. L. Oral self-administration of cocaine: Chronic excessive intake by schedule induction. Pharmacol. Biochem. Behav. 28:517–519; 1987.
27. Tang, M.; Falk, J. L. Schedule-induced oral self-administration of cocaine and ethanol solutions: Lack of effect of chronic desipramine. Drug Alcohol Dependence 25:21–25; 1990.
28. Thompson, T.; Schuster, C. R. Morphine self- administration and food-reinforced and avoidance behaviors in rhesus monkeys. Psychopharmacologia 5:87–94; 1964.
29. Unnithan, S.; Gossop, M.; Strang, J. Factors associated with relapse among opiate addicts in an out-patient detoxification programme. Br. J. Psychiatry 161:654–657; 1992.
30. Westermeyer, J. Poppies, pipes, and people. Berkeley: University of California Press; 1982.
31. Yokel, R. A. Intravenous self-administration: Response rates, the effects of pharmacological challenges and drug preferences. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987:1–33.