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BRIEF COMMUNICATION

Food Deprivation History and Cocaine Self-Administration: An Animal Model of Binge Eating

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SPECKER, S. M., S. T. LAC. AND M. E. CARROLL. *Food deprivation history and cocaine self-administration: An animal model of binge eating.* PHARMACOL BIOCHEM BEHAV **48**(4) 1025-1029, 1994.—In this two-part study, an animal model of binge eating was first produced, then the rate of acquisition of cocaine self-administration was assessed. Initially, 16 female weanling rats were food deprived (DEPR) at 25, 95, and 143 days of age. Another group of 16 age-matched controls was allowed ad lib access to food. Each time the DEPR group was food deprived, they were allowed to recover to normal weight. They were then injected with butorphanol tartrate (BUTR), an opioid that stimulates feeding, and food intake was measured for 4 h. All rats given BUTR consumed significantly more food than those given saline. Animals with DEPR history consumed food over a longer period of time, and at h 4 after BUTR injection, they consumed significantly more food than controls. In the second part of the experiment, an autoshaping procedure was used to quantitatively evaluate the rate of acquisition of cocaine self-administration. By day 30, 86% of the DEPR and 69% of the control groups had acquired cocaine self-administration.

Animal model Autoshaping Binge eating Butorphanol tartrate Cocaine Food deprivation history Intravenous Rats Self-administration

BULIMIA nervosa and binge eating are highly prevalent among young women and cause significant medical, economic, and psychiatric problems. Human literature supports a high comorbidity of bulimia nervosa and substance abuse, with rates of substance abuse in bulimia nervosa patients ranging from 25-60% and rates of bulimia nervosa in women with substance abuse ranging from 20-40% (5,9-13,15,18,19), rates much higher than in the general population (1-5%).

Animal models have been used to study such psychiatric disorders as depression, anorexia nervosa, and drug dependence (3,8,20). They offer the opportunity to examine certain aspects of these disorders that would be difficult to study in humans, such as the acquisition of drug dependence, effects of food deprivation, or a biological basis for the disorders. However, until recently, an animal model of binge eating had not been proposed (7). The lack of animal models in eating disorders may be partially explained by an emphasis in the literature that an animal model should mimic all the important aspects of human syndromes.

The goal of this research was to further develop an animal model for binge eating and to study the interaction between this component and the development of drug abuse. The binge eating model was established according to methods recently reported by Hagan and Moss (7). They briefly restricted food access in young female rats at 30, 90, and 140 days of age. After each deprivation (DEPR), body weights were allowed to return to control levels. The rats then received an injection of butorphanol (BUTR), an opioid that stimulates feeding (14), and food intake was measured. Rats with a history of deprivation continued their food intake 2 and 3 h after BUTR;

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control rats decreased their eating after the first hour. The present experiment expands on this previous model for binge eating by using a larger sample size, a longer feeding test, and by examining the subsequent rate of acquisition of cocaine self-administration.

METHOD

Subjects

Thirty-two female Sprague-Dawley (Harlan Sprague-Dawley, Madison, WI) rats that had been weaned at 21 days of age were initially housed two to a cage; however, during the second DEPR and after 120 days the rats were housed in individual cages. Unlimited access to Purina Laboratory Chow was provided when the rats were not actively engaged in a DEPR phase of the experiment. During the DEPR small amounts of chow were provided. The testing room was temperature (24°C) and humidity controlled. A standard 12 L : 12 D schedule was used with the lights on at 0700 h.

Apparatus

Octagonal operant chambers consisted of Plexiglas walls alternating with stainless steel walls. The chambers were housed in wooden enclosures for sound attenuation. A lick-operated drinking device was mounted on the stainless steel walls as was a jar containing ground food, a standard lever, a retractable lever, and stimulus lights above each lever. Constant illumination was provided by a house light at the top of the chamber. Three colored lights above the retractable lever and the inactive lever remained on during the autoshaping sessions. Details of the chamber and infusion system have been previously described (1,2).

Drugs

Cocaine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). Cocaine was mixed in sterile saline and administered at a dose of 0.2 mg/kg for each infusion. The dose was determined by infusion duration, 1 s/100 g b.wt. Butorphanol tartrate (BUTR) was provided by Bristol Laboratories (Syracuse, NY). The dose (8 mg/kg) was based on that used in previous feeding experiments (7,14). The BUTR was mixed in sterile saline just prior to each injection period. The volume of each injection ranged from 0.10–0.20 ml.

Procedure

Deprivation history. Thirty-two rats were randomly assigned into two groups consisting of 16 experimentals (DEPR) and 16 controls. There were three DEPR periods each lasting 3–18 days occurring at 25, 95, and 143 days of age. The mean weights of the control and DEPR rats were 73.1 g and 72.1 g, respectively, prior to the first deprivation. Deprivation was accomplished by limiting their food intake to approximately 3 g or 1 rat pellet. On day 2 they were 85% of the control rats' weights, and on day 3 they were at 71%. During the DEPR periods the goal was to reduce the DEPR group to 75% of controls, as reported by Hagan and Moss (7). However, mean reduction ranged from 71–78% across the three phases. During the second and third DEPR periods approximately 50% (6–12 g) of the amount of food consumed by controls (12–24 g) was provided. Free access to water was available throughout the DEPR phases.

After the first DEPR period, recovery to normal weight followed immediately with ad lib access to rat chow. The DEPR procedure was repeated for a second and third time when rats weighed 195–289 g (95 days) and 214–290 g (143 days), respectively. The time to attain 79% of the control group's mean body weight was 10 days during the second DEPR and 10–18 days to reach 75% of the original body weights in the third DEPR. Rapid weight gain occurred within 3 days of the end of the second and third DEPR stages, but it took 20 days to completely return to pre-DEPR weights.

This protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee, protocol number 9104032.

Response to opioid challenge. Rats were maintained at their fully recovered weights for 2 weeks prior to testing. Feeding tests began at 1000 h. All rats had free access to food, except that food was removed 1 h before testing. Subcutaneous injections of BUTR (8 mg/kg) or saline were administered randomly to one-half the DEPR and one-half the controls. Food intake was then measured at hours 1, 2, 3, and 4 postinjection. This process was then repeated 1 week later with saline and BUTR injections counterbalanced across DEPR and control groups. Rats that received BUTR were given saline, and those that had been given saline received BUTR. This entire procedure was again repeated in another week to control for order effect (e.g., rats that received BUTR at first injection now received saline first). A total of four injections per rat were given after each DEPR episode.

Dependent measures were body weights and amount of food consumed during the BUTR challenges. Data were analyzed using a mixed model of variance. Values of $p < 0.05$ were considered to be statistically significant.

Acquisition of cocaine self-administration. Rats were allowed 1–2 months for full recovery from the last DEPR episode. Rats were then surgically implanted with intravenous cannulas in the jugular vein according to methods described previously (1) and were placed in the operant chambers imme-

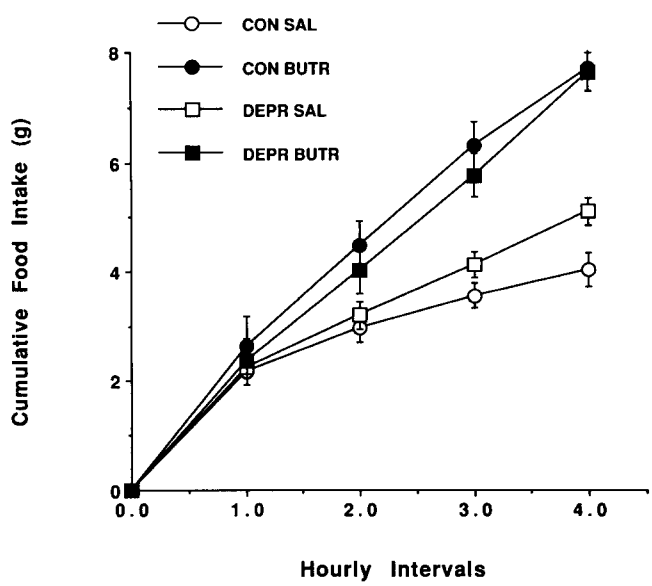

FIG. 1. Mean ± SE cumulative food intake (g) as a function of the 4-h feeding period for the four experimental conditions; control group with either saline or butorphanol (8 mg/kg) pretreatment and the deprivation group with both pretreatment conditions.

diately after the surgery. They were then allowed to recover for several days until their food and water intake had stabilized. A fixed amount (20 g) of ground rat chow was provided each day.

Several rats from the DEPR and control groups were tested simultaneously over a period of several weeks in an autoshaping procedure that has been previously described (1,2). Both groups consisted of 14 rats; two rats from each of the initial groups of 16 died or had to be removed because of tumors. An additional rat from the control group died during the autoshaping process (14 DEPR, 13 control). There were six 1-h autoshaping sessions beginning each day at 1000 h 7 days a week. Three colored lights (green, red, and yellow) above the retractable lever were illuminated during the autoshaping session and remained on until 10 infusions were delivered. At the beginning of each hour during the 6-h period, the retractable lever was extended into the chamber on a random interval schedule with a mean of 60 s and range of 30–90 s. The lever was retracted if the animal touched it or after 15 s. A cocaine infusion (0.2 mg/kg) was subsequently delivered 6 s after each lever retraction.

Each day following the 6-h autoshaping session there was a 6-h cocaine self-administration session when the lever remained extended and the lights above the lever were illuminated every time an infusion occurred. Each lever press resulted in a cocaine infusion (0.2 mg/kg). Three colored lights over the inactive lever were illuminated every time the lever was pressed and responses on this lever were counted. A time-out began after the 6-h self-administration period and extended until the start of the next day's session (1000 h). During the time-out the lever was retracted, no cocaine was available, and the lights above the levers were off. The animals' daily food allotment (20 g) was provided during this time and water was freely available.

The criterion for acquisition of cocaine self-administration was 5 consecutive days during which the mean number of infusions during the 6-h self-administration period was 100 or more. If this criterion was not met by 30 days, the experiment was terminated, and it was designated that the rat did not acquire. Dependent measures that were analyzed were number of days to meet autoshaping criterion, number of infusions during the self-administration phase, and responses on the inactive lever. A nonparametric survival analysis (4) using the Lee-Desu statistic was conducted and values of $p < 0.05$ were considered to be statistically significant.

RESULTS

Deprivation History

The end of the DEPR periods was determined by comparison to controls in the first two DEPR because of expected weight gain as they grew. However, reductions in the third DEPR phase were based on each rat's own baseline weight because weights had stabilized by that time and there was a wider weight range among individual rats in the DEPR group (214–290 g).

Response to opioid challenge. The results obtained after the second and third DEPR episodes were similar, and they were combined as were results from the two trials because no order effects were found. Figure 1 shows the cumulative amounts of food consumed by the groups, with and without drug treatment. Rats consistently ate more during the first hour than any subsequent hour ($p < 0.05$). By the end of the second hour it was apparent that BUTR treatment consistently resulted in more food consumption than after saline injections ($p < 0.05$), and the pattern of accelerated food intake continued throughout the third and fourth hours. However, no difference in cumulative food intake was found by the end of the

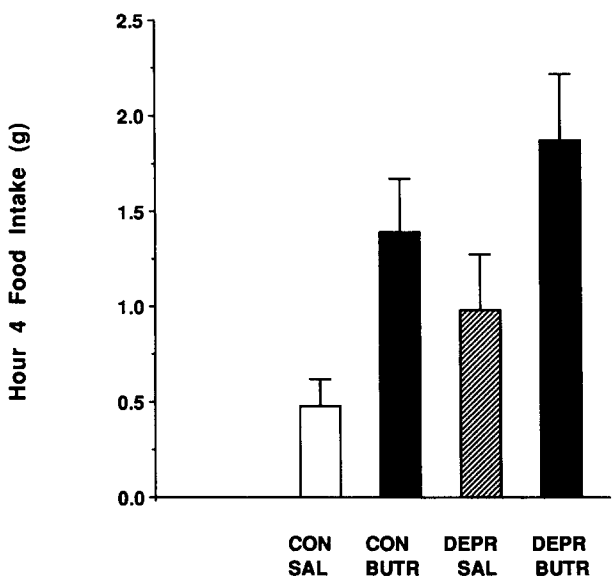

FIG. 2. Mean ± SE fourth hour food intake (g) for the four experimental conditions; control group with either saline or butorphanol (8 mg/kg) pretreatment and the deprivation group with both pretreatment conditions.

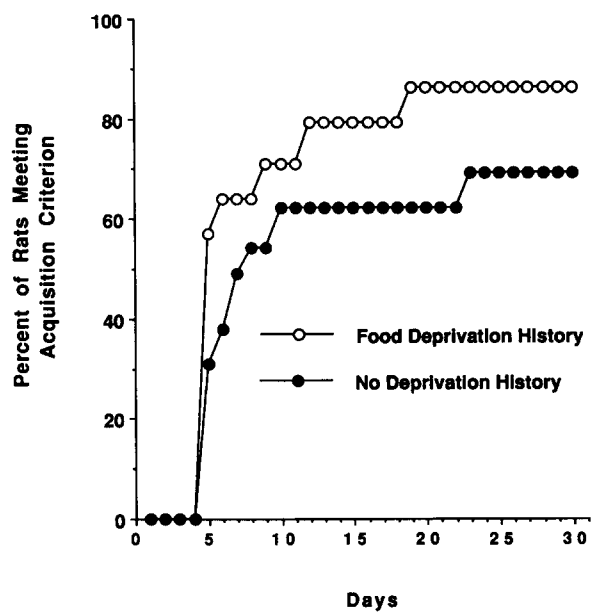

FIG. 3. Percent of total rats in each group presented as a function of the 30 days allowed for acquisition of cocaine self-administration for both the deprivation history ($N = 14$) and control groups ($N = 13$). Each point represents the percent of rats in each group that had met the acquisition criterion. The criterion was defined as 5 consecutive days when the mean number of infusions per day during the 4-h self-administration sessions was 100 or more.

fourth hour between control and DEPR groups that received BUTR (7.69 vs. 7.62 g, respectively), possibly due to ceiling effect.

Figure 2 shows the food consumption during hour 4 for the DEPR and control groups under conditions of BUTR and saline injections. Rats receiving BUTR consumed significantly more food than rats receiving saline ($p < 0.05$) at all hours cumulatively and during hour 4. Although overall there were statistically significant differences between the DEPR groups and the control groups and under BUTR vs. saline conditions, no drug × group interaction was found.

Acquisition of Cocaine Self-Administration

The second part of the experiment examined acquisition rates of cocaine self-administration among the DEPR and control groups (Fig. 3). Of the 14 completers in the DEPR group, nine rapidly met the autoshaping criterion; that is, they self-administered cocaine at an average of 100 infusions/6-h session over 5 consecutive days by the sixth day in the autoshaping chamber. Only five of the 13 rats in the control group acquired this behavior by day 6. There were three rats in the DEPR group and four in the control group that met the acquisition criteria between 7 and 23 days. There were two in the DEPR and four in the control group that either just met the acquisition criteria at 30 days or reached 30 days without acquiring cocaine self-administration. Although a clear trend toward more rapid acquisition is seen in those with a history of deprivation, the rates of acquisition were not statistically significant ($p > 0.05$)

DISCUSSION

Three effects were found in the present study: BUTR enhances feeding, a history of DEPR enhances feeding, and a there was a trend for more rapid acquisition of cocaine self-administration in the DEPR group. The phenomenon of opioids enhancing feeding has been described previously (6, 14,17). The present study found a clear overall increase in feeding after BUTR, in contrast to Hagen and Moss (7), who did not find an increase in cumulative feeding with BUTR. The difference between their results and the present findings may be attributed to a smaller sample size ($n = 13$ vs. 32) and shorter duration of experiment (3 h vs. 4 h).

The present experiment also sought to determine whether a history of food deprivation would alter the response to BUTR. The results indicate that a history of food deprivation increased the response to BUTR, but not until the fourth hour after the BUTR injection. The effect of the combined deprivation history and drug effect was to lengthen the feeding episode rather than to increase the rate of feeding. This finding was consistent with those reported by Hagen and Moss (7). There was also an increase in subsequent feeding as a result of food deprivation history when rats received saline injections. This finding is similar to that reported by Coscina and Dixon (3).

The prolonged feeding in animals with a food deprivation history is similar in several respects to the binge eating found in bulimia nervosa patients, thus supporting this technique as an animal model of binge eating. In humans, it is often noted clinically that eating disorders begin with food restriction and fasting, later developing into binge eating and purging (16).

In the second part of the experiment the drug self-administration acquisition model was used to determine if binge eating rats with a history of food deprivation would develop cocaine-reinforced behavior more rapidly than control rats. Although the rats with a food deprivation history acquired cocaine self-administration at a slightly higher rate than controls, this finding failed to reach statistical significance due to the small sample size and high variability. Further research directed toward this topic should utilize larger numbers of animals. It would also be interesting to examine gender and number, and severity or duration of the DEPR periods as additional variables contributing to the effect. These results present an animal model that may be used to increase our understanding of certain eating and drug use patterns in humans.

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REFERENCES

1. Carroll, M. E.; Boe, I. N. Increased intravenous drug self-administration during deprivation of other reinforcers. Pharmacol. Biochem. Behav. 17:563–567; 1982.
2. Carroll, M. E.; Lac, S. T. Autoshaping IV cocaine self-administration in rats: Effect of nondrug alternative reinforcers on acquisition. Psychopharmacology (Berlin) 110:5–12; 1993.
3. Coscina, D. V.; Dixon L. M. Body weight regulation in anorexia nervosa: Insights from an animal model. In: Padraig, L., ed. Anorexia nervosa: Recent developments in research. New York: A. R. Liss; 1983:207–219.
4. Cox, R. D.; Oakes, D. Analysis of survival data. London: Chapman and Hall; 1984.
5. Goldbloom, D. S.; Naranjo, C. A.; Bremner, K. E.; Hicks, L. K. Eating disorders and alcohol abuse in women. Br. J. Addict. 87(6):913–919; 1992.
6. Gosnell, B. A.; Levine, A. S.; Morley, J. E. The stimulation of food intake by selective agonists of mu, kappa and delta opioid receptors. Life Sci. 38:1081–1088; 1986.
7. Hagan, M. M.; Moss, D. E. An animal model of bulimia nervosa: Opioid sensitivity to fasting episodes. Pharmacol. Biochem. Behav. 39(2):421–422; 1991.
8. Henn, F. A.; McKinney, W. T. Animal models in psychiatry. In: Meltzer, H. Y., ed. Psychopharmacology: The third generation of progress. New York: Raven Press; 1987:687–695.
9. Hudson, J. I.; Pope, H. G.; Yurgelun-Todd, D.; Jonas, J. M.; Frankenburg, F. R. A controlled study of lifetime prevalence of affective and other psychiatric disorders in bulimic outpatients. Am. J. Psychiatry 144:1283–1287; 1987.
10. Hudson, J. I.; Weiss, R. D.; Pope, H. G.; McElroy, S. K.; Mirin, S. M. Eating disorders in hospitalized substance abusers. Am. J. Drug Alcohol Abuse 18(1):75–85; 1992.
11. Jonas, J.; Gold, M. S.; Sweeney, D.; Pottash, A. Eating disorders and cocaine abuse: A survey of 259 cocaine abusers. J. Clin. Psychiatry 48:47–50; 1987.
12. Jonas, J. M. Do substance-abuse, including alcoholism, and bulimia covary? In: Reid, L. D., ed. Opioids, bulimia and alcoholism. New York: Springer-Verlag; 1990:247–258.
13. Lacey, J. H.; Moureli, E. Bulimic alcoholics: Some findings of a clinical subgroup. Br. J. Addict. 81:389–393; 1986.
14. Levine, A. S.; Morley, J. E. Butorphanol tartrate induces feeding in rats. Life Sci. 32:781–785; 1983.
15. Mitchell, J. E.; Hatsukami, D.; Eckert, E. D.; Pyle, R. L. Characteristics of 275 patients with bulimia. Am. J. Psychiatry 142: 482–485; 1985.

16. Mitchell, J. E.; Hatsukami, D.; Pyle, R. L.; Eckert, E. D. The bulimia syndrome: Course of the illness and associated problems. Compr. Psychiatry 27:165–170; 1986.
17. Morley, J. E.; Parker, S.; Levine, A. S. Effect of butorphanol tartrate on food and water consumption in humans. Am. J. Clin. Nutr. 42:1175–1178; 1985.
18. Newman, M. M.; Gold, M. S. Preliminary findings of patterns of substance abuse in eating disorder patients. Am. J. Drug Alcohol Abuse 18(2):207–211; 1992.
19. Peveler, R.; Fairburn, C. Eating disorders in females who abuse alcohol. Br. J. Addiction 85:1633–1638; 1990.
20. Smith, G. P. Animal models of human eating disorders. Ann. NY Acad. Sci. 575:63–74; 1989.