Pharmacology Biochemistry and Behavior, Vol. 44, pp. 919–924, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

Morphine-induced Feeding: A Comparison of the Lewis and Fischer 344 Inbred Rat Strains

BLAKE A. GOSNELL[1] AND DEAN D. KRAHN

Department of Psychiatry, University of Wisconsin-Madison, Parkway Hospital, 6001 Research Park Boulevard, Madison, WI 53719

Received 3 August 1992

GOSNELL, B. A. AND D. D. KRAHN. *Morphine-induced feeding: A comparison of the Lewis and Fischer 344 inbred rat strains.* PHARMACOL BIOCHEM BEHAV 44(4) 919–924, 1993.—Rats of the Lewis inbred strain have been shown to self-administer more morphine than rats of the inbred Fischer 344 (F344) strain. Because morphine reward and opioid-induced feeding may involve a common mechanism, we measured whether these strains also differ in their feeding response to morphine. In Experiment 1, rats were maintained on powdered rat chow and given SC injections of morphine sulfate (1, 3, and 10 mg/kg) and saline; all rats were tested with all doses. Food intake was measured 2, 4, and 6 h after injection. In Experiment 2, rats were given a choice of two diets: a fat/protein diet and a carbohydrate/protein diet. Feeding responses to morphine were measured in a manner identical to that in Experiment 1. In both experiments, the feeding response to morphine was greater in Lewis rats than in F344 rats. To determine whether these responses might be explained by differences in the levels of morphine achieved in the blood or brain, rats of each strain were given SC injections of morphine sulfate (3 mg/kg) and sacrificed either 30 min or 3 h after injection. Serum and brain morphine levels were determined by radioimmunoassay. Lewis rats had significantly less brain morphine than F344 rats at 30 min; they did not differ in morphine content at 3 h. Serum levels were similar at 30 min; at 3 h, F344 rats had slightly lower levels than Lewis rats. Thus, differences in tissue levels cannot readily explain the differences in feeding responses to morphine. These results indicate a strain difference in the feeding response to morphine that complements previously observed differences between Lewis and Fischer 344 rats in the self-administration of morphine. Further comparisons of these two strains may be useful in assessing the contribution of altered reward mechanisms to both eating disorders and drug abuse.

Morphine Opioid Lewis rat Fischer 344 rat Inbred rats Feeding Food intake Diet selection

COMPARISONS of different strains or genotypes of rats or mice have provided some insights into the mechanisms controlling drug self-administration (6,13,17) One such comparison is that of rats of the inbred Lewis strain with Fischer 344 (F344) inbred rats. When compared to F344 rats, Lewis rats self-administer more alcohol (21), cocaine (6), and etonitazene (22) and have a higher preference for morphine and codeine (23). Lewis rats also develop a stronger conditioned place preference to morphine and cocaine than do F344 rats (24). Thus, the two strains apparently differ in their sensitivity to morphine and cocaine. Beitner-Johnson et al. (1) found that Lewis and F344 rats differed in levels of morphine- and cocaine-sensitive phosphoproteins in the ventral tegmental area (VTA) but not in the substantia nigra. The VTA is the origin of neurons in the mesolimbic dopaminergic system, which has been implicated in mediating the rewarding effects of opiates, cocaine, alcohol, and possibly food, water, and palatable fluids (5,9,14,26–28). Beitner-Johnson et al. (1) suggested that strain differences in phosphoproteins in this area may be related to strain differences in drug preference.

It is well known that opioid agonists, under certain conditions, cause an increase in food intake (4,7,12,16). This effect is thought to be due, at least in part, to an opioid-mediated increase in the palatability or reward value of food (4,16). Because the rewarding effects of morphine and food may be mediated by the same system, and morphine is also thought to increase food intake by enhancing food reward, rats with increased sensitivity to morphine reward may also display a relatively greater feeding response to morphine. We tested this possibility with rats maintained on lab chow and with rats maintained on a dietary self-selection regimen. To test the possibility that any observed differences were due to differential distribution or elimination of the drug, morphine levels in the serum and brain were also measured after administration of a single dose.

[1] To whom requests for reprints should be addressed.

EXPERIMENT 1: EFFECTS OF MORPHINE IN RATS MAINTAINED ON LAB CHOW

METHOD

Male Lewis and F344 rats were purchased from Harlan-Sprague-Dawley, Inc. (Indianapolis, IN). They were individually housed in stainless steel cages and given food and water ad lib. The food (Purina Lab Chow #5001) was presented in powdered form in glass jars attached to the floors of the cages. The lights were on from 7:00 a.m.-7:00 p.m., and all procedures were initiated in the first half of the light period. The experiment began 5 days after rats were received, at which time Lewis rats weighed 256 ± 3 g and F344 rats weighed 250 ± 3 g. Rats were given SC injections of morphine sulfate at doses of 0 (vehicle), 1, 3, or 10 mg/kg. Morphine (Mallinckrodt, Inc., St. Louis, MO) was obtained from the National Institute on Drug Abuse (Rockville, MD). The vehicle was 0.9% saline solution. Rats were returned to their home cages immediately after injection, and food intake was determined by weight 2, 4, and 6 h after injection. On test days, water was presented in 100-ml graduated cylinders; intake was measured at 2, 4, and 6 h postinjection. The test procedure was repeated three additional times (2 days apart) in an identical manner, such that each rat was tested with each dose. Injection sequences were varied across rats. At each time point, cumulative intakes were analyzed with a two-factor analysis of variance (dose × strain). Within each strain, intakes after administration of the three doses were compared to the control condition with Dunnett's tests (one tailed). For each of these comparisons, error terms were based only upon the groups being compared.

RESULTS

Food Intake

Food intake was significantly increased by morphine in both strains (Fig. 1). The dose effect was significant at 2 and 4 h, $F(3, 66) = 16.07$ and 5.15, respectively, $p < 0.01$. In general, the increases above baseline were greater in Lewis than in F344 rats. At 4 h, this increase was approximately 1.0 g in Lewis rats and approximately 0.5 g in F344 rats. There was also a significant overall strain effect at 2, 4, and 6 h, $F(1, 22) = 18.94$, 40.69, and 68.51, respectively, $p < 0.001$, and a significant dose × strain interaction at 2 h, $F(3, 66) = 3.54$, $p < 0.05$. At 6 h, there were no significant increases above baseline in either strain (not shown).

Water Intake

The pattern of water intake across doses and strains resembled that of food intake. There was a significant dose effect at 2, 4, and 6 h, $F(3, 66) = 17.02$, 19.05, and 32.46, respectively, $p < 0.001$. There were also significant strain effects at 2, 4, and 6 h, $F(1, 22) = 11.47$, 16.53, and 14.29, respectively, $p < 0.005$. The dose × strain interaction was significant at 4 h, $F(3, 66) = 3.03$, $p < 0.05$, and approached significance at 2 and 6 h ($0.05 < p < 0.10$). As with food intake, the increases above baseline were in general greater in Lewis rats than in F344 rats. The pattern of results at 6 h (not shown) was similar to that observed at 4 h.

EXPERIMENT 2: EFFECTS OF MORPHINE IN RATS GIVEN A CHOICE OF DIETS

METHOD

Lewis and F344 rats were housed under the same conditions as described in Experiment 1. Upon receipt, they were given water and standard lab chow ad lib. Four days later, the lab chow was removed and each rat was given ad lib access to two diets: a high-fat diet and a high-carbohydrate diet. When equated on the basis of energy, the diets contained equal amounts of protein, vitamins, minerals, and fiber. The compositions of these diets are presented in Table 1. The diets were presented in glass jars bolted to the floors of the cages. To prevent the formation of position preferences, the positions of the jars were reversed daily. Daily intakes of the two diets were measured on days 7, 8, and 9 of the diet adaptation period. After 10 days of adaptation to the diets, morphine trials were conducted in a manner similar to that described in Experiment 1. One exception is that water intake was not measured. Mean body weight (± SEM) at the beginning of the morphine trials was 276 ± 3 g for Lewis rats and 251 ± 4 g for F344 rats. Intake data for each diet, as well as for total caloric intake, were analyzed as described in Experiment 1.

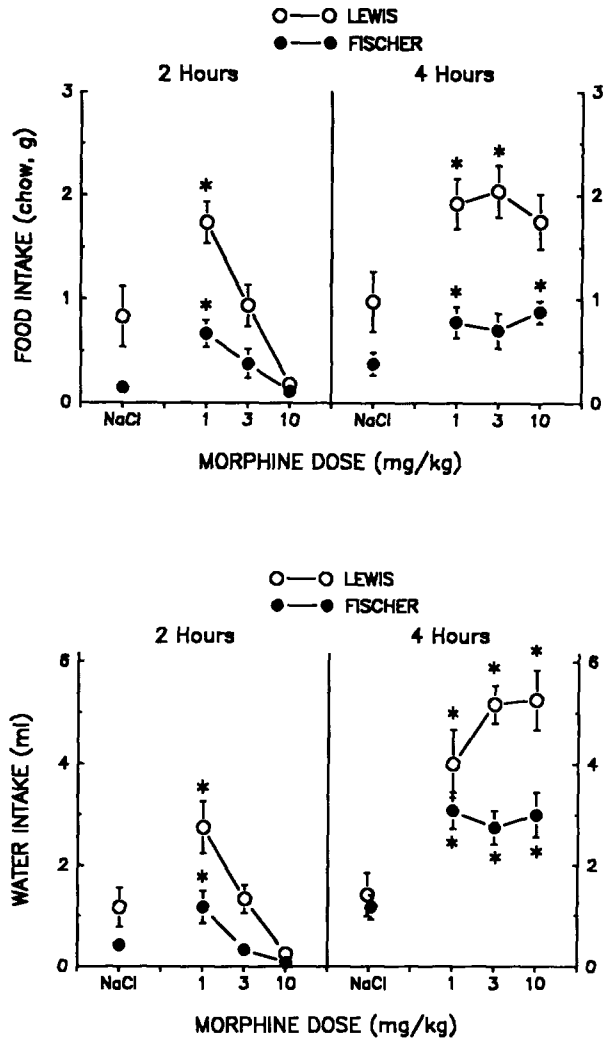

FIG. 1. Two- and 4-h cumulative food and water intake (means ± SEM) of Lewis and F344 rats after SC injections of morphine sulfate ($n = 12$/strain). *Significant differences from the corresponding control (NaCl) condition (Dunnett's test, $p < 0.05$, one tailed).

TABLE 1
COMPOSITION OF DIETS USED IN EXPERIMENT 2

	Diet	
	Carbohydrate/Protein	Fat/Protein
Corn starch	917.9	–
Dextrin	458.8	–
Sucrose	152.9	–
Casein*	429.2	429.2
DL-methionine	6.5	6.4
Vegetable shortening	–	578.0
Safflower oil	–	101.8
AIN-76A vitamin mix†	19.9	19.9
AIN-76 mineral mix†	70.0	69.8
Choline chloride	5.0	5.0
Cellulose (Alphacel)	99.8	100.0
Weight (g)	2,160.0	1,310.1
Total energy (kcal)‡	7800	7800
Energy density (kcal/g)	3.61	5.95

All components are expressed as weight (g).
*Assuming a protein content of 90%.
†The vitamin and mineral mixes contain 97 and 12% sucrose, respectively.
‡Based upon energy values of 4, 9, and 4 kcal/g for carbohydrate, fat, and protein.

RESULTS

Baseline Diet Preferences

Prior to morphine testing, F344 rats consumed significantly more of the fat diet than did Lewis rats [24 ± 4 kcal vs. 11 ± 4 kcal, $t(22) = 2.08, p < 0.05$]. F344 rats in general consumed less of the carbohydrate diet than did Lewis rats, although the difference fell just short of significance [48 ± 4 kcal vs. 58 ± 3 kcal, $t(22) = 1.91$, $0.05 < p < 0.10$]. The percentage of total calories consumed from the fat diet was significantly greater for F344 rats (33 ± 6%) than for Lewis rats (16 ± 5%), $t(22) = 2.20, p < 0.05$. Mean daily caloric intakes of the two strains did not differ (72 ± 1 kcal for F344 rats vs. 70 ± 2 kcal for Lewis rats).

Total Intake

Morphine stimulated total intake in Lewis but not F344 rats. This observation is supported by the analyses of variance, which indicated a significant dose effect at 2 and 4 h, $F(3, 66) = 12.26$ and 2.83, respectively, $p < 0.05$, and a significant dose × strain interaction at 2, 4, and 6 h, $F(3, 66) = 3.42$, 2.80, and 3.32, respectively, $p < 0.05$. The strain effect was significant at 6 h, $F(1, 22) = 5.58, p < 0.05$, and near significance at 4 h, $F(1, 22) = 4.27, p = 0.051$. As was found in Experiment 1, only the 1-mg/kg dose stimulated 2-h intake (Lewis rats only). All three doses significantly increased 4-h intake in Lewis rats; total intake was not increased in F344 rats (Fig. 2). Six-hour results (not shown) were similar to those at 4 h in that all three doses increased intake in Lewis but not F344 rats.

Carbohydrate Diet

Significant increases in carbohydrate intake after morphine treatment were observed only in Lewis rats (Fig. 2). There was

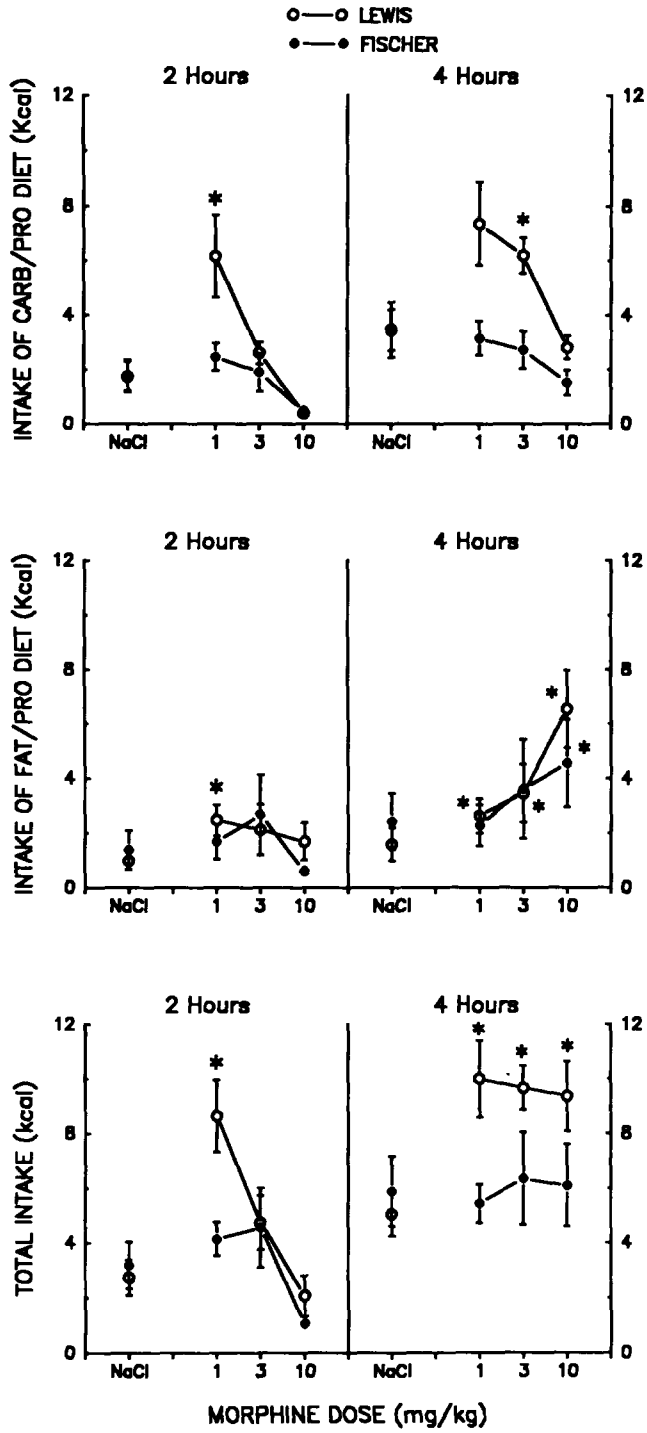

FIG. 2. Two- and 4-h cumulative intake of a high-carbohydrate diet (upper panel), a high-fat diet (middle panel), and total caloric intake (lower panel) by Lewis and F344 rats after SC injections of morphine sulfate (means ± SEM) (n = 12/strain). *Significant differences from the corresponding control (NaCl) condition (Dunnett's test, $p < 0.05$, one tailed).

a significant dose effect at 2 and 4 h, $F(3, 66) = 11.44$ and 7.22, $p < 0.001$, and a significant dose × strain interaction at 2 and 4 h, $F(3, 66) = 3.55$ and 3.83, $p < 0.05$. The strain effect was significant at 4 and 6 h, $F(1, 22) = 7.62$ and 7.02, $p < 0.05$, and approached significance at 2 h ($p < 0.06$). At 6 h, there were no significant increases above baseline in either strain (not shown).

Fat Diet

There were no significant differences between strains in the intake of the high-fat diet. The dose effect was significant at 4 and 6 h, $F(3, 66) = 8.53$ and 10.86, $p < 0.001$. No other effects or interactions were significant. Only the 10-mg/kg dose increased intake in F344 rats, whereas all three doses increased intake in Lewis rats (Fig. 2). Results at 6 h (not shown) were similar to those at 4 h.

EXPERIMENT 3: DETERMINATION OF SERUM AND BRAIN MORPHINE LEVELS

METHOD

Male Lewis and F344 rats were obtained and housed as described in Experiment 1. Seven days after receipt, each rat was given a single injection of morphine sulfate (3 mg/kg, SC). At the time of injection, Lewis rats weighed 285 ± 2 g and F344 rats weighed 264 ± 2 g. They were returned to their home cages after injection and sacrificed by decapitation either 30 min or 3 h later. Brains and trunk blood were collected for determination of morphine content. The blood was centrifuged at 3,000 rpm for 10 min at 4°C; the serum was then diluted 1 : 4 with previously collected serum from noninjected rats of the same strain. The samples were frozen at −80°C until assayed. Whole brains were weighed and homogenized in a sodium phosphate buffer (pH 8.9, 2 ml/g wet brain). The homogenate was centrifuged at 9,990 × *g* for 10 min at 4°C. One milliliter of the supernatant was removed and centrifuged again with the same parameters. These samples were then stored at −80°C until assay. Assays were performed with an assay kit for serum morphine (Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA). Iodinated morphine was added, along with the sample, to tubes precoated with antibodies to morphine. All samples and standards were tested in duplicate. After a 1-h incubation period at room temperature, the tubes were decanted and radioactivity was counted on a gamma counter. Standards were prepared by adding known quantities of morphine sulfate to serum from noninjected rats from each strain. Standards for brain samples were prepared by adding morphine to the supernatant of brains (prepared as described above) from noninjected rats of each strain. Concentrations of morphine in the samples were calculated from the line (logit-log) fitted to the appropriate set of standards. In transforming the results of the brain assays from ng/ml to ng/g of wet weight, 76% of the wet weight was considered to be due to water. This value was determined from the dry weight to wet weight ratio in three Sprague-Dawley rat brains in a separate experiment. For each time point, tissues from the two strains were compared with *t*-tests (two tailed).

RESULTS

Thirty minutes after injection, Lewis rats had a significantly lower brain concentration of morphine than did F344 rats [57.7 ± 1.8 vs. 84.1 ± 2.3 ng/g brain (wet weight), $t(10) = 8.98$, $p < 0.01$]. At 3 h, the brain levels were similar (12.6 ± 0.9 for Lewis vs. 16.1 ± 3.2 ng/g for F344 rats, $p > 0.05$). In contrast, serum levels did not differ at 30 min (307.5 ± 15.1 for Lewis vs. 306.2 ± 26.9 ng/ml for F344 rats). At 3 h, Lewis rats had serum values of 9.0 ± 1.3 ng/ml and F344 rats 6.6 ± 2.7 ng/ml. These values are not significantly different. However, the F344 group had one extreme value (19.5 ng/ml). Excluding this value, the mean for the F344 group at 3 h was 4.0 ± 1.0 ng/ml, significantly less than the Lewis value, $t(9) = 2.97$, $p < 0.05$.

GENERAL DISCUSSION

The effects of opioids on feeding are thought to involve changes in the rewarding value of food (4,16). Inasmuch as Lewis and F344 rats have been shown to be differentially sensitive to morphine reward (23,24), it was predicted that they would differ in their feeding response to morphine. This prediction was confirmed in experiments with rats fed lab chow and with rats allowed to self-select from high-fat and high-carbohydrate diets.

One potential explanation for differential responses to a drug is that there is a differential metabolism, distribution, or elimination of the drug. We tested this possibility by measuring brain and serum levels of morphine in the two strains at two time points. A 3-mg/kg dose was used for these measurements because it is intermediate to the high and low doses tested in the feeding experiments. Doses of 1, 3, and 10 mg/kg all had approximately equal effects on food intake. At 30 min, the strains did not differ in serum morphine levels. At 3 h, a time selected because it is in the middle of the interval where most feeding occurred (2–4 h), serum morphine levels were slightly lower in F344 rats compared to Lewis rats. Because the effect of opioids on food intake is thought to be a central effect (7), brain levels of morphine may be a more relevant comparison. At 30 min, Lewis rats actually had lower morphine levels than F344 rats; the strains did not differ at 3 h. It is possible that a larger feeding response could result from the fact that lower brain levels produced less catalepsy or other behavior that might compete with or interfere with feeding. However, doses of morphine both higher and lower than the test dose (3 mg/kg) were approximately equally effective in stimulating food intake. Thus, it may be that rate of entry into the brain is an important variable in morphine-induced feeding. Lewis rats had lower morphine levels at 30 min but approximately equal levels at 3 h. The effect of rate of entry cannot be determined from the present results; a more detailed study of this issue may yield important information about the nature of opioid-induced feeding.

We previously reported that the effect of morphine on diet selection is dependent upon baseline diet preferences (8). Based upon these results, it would have been predicted in the current study that morphine would have the greatest stimulatory effect on the intake of the carbohydrate diet, as both strains displayed a baseline preference for this diet. This was the case for Lewis rats when given the 1- and 3-mg/kg doses; the 10-mg/kg dose stimulated only fat intake. We had noted in the previous article, however, that superimposed on the effect of baseline preferences was a tendency for lower doses to be more effective in stimulating carbohydrate intake and for higher doses to be more effective in increasing fat intake. In the present results, this qualitative dose effect appears to be stronger than the effect of baseline diet preference. In addition, the previous report was based upon a larger group of rats divided into groups based upon baseline diet preferences, whereas the present results are based upon smaller groups

that were not divided further. Regardless of the influence of baseline diet preferences, however, the effect of morphine was larger in Lewis rats than F344 rats, as demonstrated by the greater increase in total caloric intake in both Experiments 1 and 2.

It should be noted that Lewis and F344 rats differ in ways other than drug preferences or responses to morphine. Compared to F344 rats, female Lewis rats are more susceptible to streptococcal cell wall-induced arthritis (25). This susceptibility appears to be due in part to a relative deficiency in the synthesis and release of hypothalamic corticotropin-releasing hormone in Lewis rats (18,20), which results in blunted pituitary and adrenocortical responses to physical stressors and inflammatory mediators (18,19). The two strains also differ in the mechanism by which catecholamine-synthesizing enzyme activities in the adrenal are increased in response to repeated immobilization stress (3).

Manipulations that alter glucocorticoid levels have been shown to alter food intake and diet selection (2,10). The aforementioned strain differences in the hypothalamic-pituitary-adrenal (HPA) axis, therefore, may contribute to the observed differences in morphine-induced feeding. However, McLean and Hoebel (15) found no effect of adrenalectomy or dexamethasone treatment on the feeding response to hypothalamic injections of [D-ala^2]-methionine-enkephalinamide. Levine and Morley (11) reported that the feeding response to the opioid agonist ethylketocyclazocine was enhanced in adrenalectomized rats. This effect, however, was attributed primarily to the removal of the adrenal medulla, as corticosterone replacement did not normalize the response, and enhancement was also observed in adrenal-demedullated rats. These studies suggest, then, that differences in HPA axis responsivity cannot account for the present results.

In summary, the published comparisons of Lewis and F344 rats led us to hypothesize that Lewis rats would display a larger feeding response to morphine. In two experiments, morphine produced greater feeding and drinking responses in Lewis rats than in F344 rats. This strain difference could not be readily explained by differences in serum or brain levels of morphine measured at two time points. Further comparisons of these two strains may be useful in assessing the contribution of altered reward mechanisms to both eating disorders and drug abuse.

ACKNOWLEDGEMENTS

This research was performed at the University of Michigan and was supported by NIDA Grants DA05471 and DA06827. The authors thanks Dr. M. Hariharan, Steve Dove, Chetan Patel, Charles Ryan, and Ted Van Noord for their technical assistance.

REFERENCES

1. Beitner-Johnson, D.; Guitart, X.; Nestler, E. J. Dopaminergic brain reward regions of Lewis and Fischer rats display different levels of tyrosine hydroxylase and other morphine- and cocaine-regulated phosphoproteins. Brain Res. 561:147–150; 1991.
2. Castonguay, T. W.; Dallman, M. F.; Stern, J. S. Some metabolic and behavioral effects of adrenalectomy on obese Zucker rats. Am. J. Physiol. 251:R923–R933; 1986.
3. Cooper, D. O.; Stolk, J. M. Differences between inbred rat strains in the alteration of adrenal catecholamine synthesizing enzyme activities after immobilization stress. Neuroscience 4: 1163–1172; 1979.
4. Cooper, S. J.; Jackson, A.; Kirkham, T. C.; Turkish, S. Endorphins, opiates and food intake. In: Rodgers, R. J.; Cooper, S. J., eds. Endorphins, opiates and behavioral processes. New York: John Wiley and Sons; 1988:143–186.
5. Di Chiara, G.; Acquas, E.; Carboni, E. Drug motivation and abuse: A neurobiological perspective. Ann. NY Acad. Sci. 654: 207–219; 1992.
6. George, F. R.; Goldberg, S. R. Genetic differences in responses to cocaine. In: Clouet, D.; Asghar, K.; Brown, R., eds. Mechanisms of cocaine abuse and toxicity. NIDA Research Monograph 88. Rockville, MD: NIDA; 1988:239–249.
7. Gosnell, B. A. Central structures involved in opioid-induced feeding. Fed. Proc. 46:163–167; 1987.
8. Gosnell, B. A.; Krahn, D. D.; Majchrzak, M. J. The effects of morphine on diet selection are dependent upon baseline diet preferences. Pharmacol. Biochem. Behav. 37:207–212; 1990.
9. Hernandez, L.; Hoebel, B. G. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci. 42:1705–1712; 1988.
10. Kumar, B. A.; Leibowitz, S. F. Impact of acute corticosterone administration on feeding and macronutrient self-selection patterns. Am. J. Physiol. 254:R222–R228; 1988.
11. Levine, A. S.; Morley, J. E. Adrenal modulation of opiate induced feeding. Pharmacol. Biochem. Behav. 19:403–406; 1983.
12. Levine, A. S.; Morley, J. E.; Gosnell, B. A.; Billington, C. J.; Bartness, T. J. Opioids and consummatory behavior. Brain Res. Bull. 14:663–672; 1985.
13. Li, T.-K.; Lumeng, L.; McBride, W. J.; Waller, M. B. Progress toward a voluntary oral consumption model of alcoholism. Drug Alcohol Depend. 4:45–60; 1979.
14. Mark, G. P.; Blander, D. S.; Hoebel, B. G. A conditioned stimulus decreases extracellular dopamine in the nucleus accumbens after the development of a learned taste aversion. Brain Res. 551: 308–310; 1991.
15. McLean, S.; Hoebel, B. G. Opiate and norepinephrine-induced feeding from the paraventricular nucleus of the hypothalamus are dissociable. Life Sci. 31:2379–2382; 1982.
16. Reid, L. D. Endogenous opioid peptides and regulation of drinking and feeding. Am. J. Clin. Nutr. 42:1099–1132; 1985.
17. Sinclair, J. D.; Le, A. D.; Kiianmaa, K. The AA and ANA rat lines, selected for differences in voluntary alcohol consumption. Experientia 45:798–805; 1989.
18. Sternberg, E. M.; Glowa, J. R.; Smith, M. A.; Calogero, A. E.; Listwak, S. J.; Aksentijevich, S.; Chrousos, G. P.; Wilder, R. L.; Gold, P. W. Corticotropin releasing hormone related behavioral and neuroendocrine responses to stress in Lewis and Fischer rats. Brain Res. 570:54–60; 1992.
19. Sternberg, E. M.; Hill, J. M.; Chrousos, G. P.; Kamilaris, T.; Listwak, S. J.; Gold, P. W.; Wilder, R. L. Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats. Proc. Natl. Acad. Sci. USA 86:2374–2378; 1989.
20. Sternberg, E. M.; Young, W. S., III; Bernardini, R.; Calogero, A. E.; Chrousos, G. P.; Gold, P. W.; Wilder, R. L. A central nervous system defect in biosynthesis of corticotropin-releasing hormone is associated with susceptibility to streptococcal cell wall-induced arthritis in Lewis rats. Proc. Natl. Acad. Sci. USA 86:4771–4775; 1989.
21. Suzuki, T.; George, F. R.; Meisch, R. A. Differential establishment and maintenance of oral ethanol reinforced behavior in Lewis and Fischer 344 inbred rat strains. J. Pharmacol. Experiment Ther. 245:164–170; 1988.
22. Suzuki, T.; George, F. R.; Meisch, R. A. Etonitazene delivered orally serves as reinforcer for Lewis but not Fischer 344 rats. Pharmacol. Biochem. Behav. 42:579–586; 1992.
23. Suzuki, T.; Otani, K.; Koike, Y.; Misawa, M. Genetic differences in preferences for morphine and codeine in Lewis and Fischer 344 inbred rat strains. Jpn. J. Pharmacol. 47:425–431; 1988.

24. Terwilliger, R. Z.; Bradbury, C.; Guitart, X.; Beitner-Johnson, D.; Marby, D.; Kosten, T. A.; Roth, R. H.; Nestler, E. J. Lewis and Fischer 344 rats and drug addiction: Behavioral and biochemical correlates. Soc. Neurosci. Abstr. 17:823; 1991.
25. Wilder, R. L.; Calandra, G. B.; Garvin, A. J.; Wright, K. D.; Hansen, C. T. Strain and sex variation in the susceptibility to streptococcal cell wall-induced polyarthritis in the rat. Arthritis Rheum. 25:1064–1072; 1982.
26. Wise, R. A. The role of reward pathways in the development of drug dependence. Pharmacol. Ther. 35:227–263; 1987.
27. Wise, R. A.; Hoffman, D. C. Localization of drug reward mechanisms by intracranial injections. Synapse 10:247–263; 1992.
28. Yoshida, M.; Yokoo, H.; Mizoguchi, K.; Kawahara, H.; Tsuda, A.; Nishikawa, T.; Tanaka, M. Eating and drinking cause increased dopamine release in the nucleus accumbens and ventral tegmental area in the rat: Measurement by in vivo microdialysis. Neurosci. Lett. 139:73–76; 1992.