Pergamon

Pharmacology Biochemistry and Behavior, Vol. 49, No. 2, pp. 377–383, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0174-G

Naloxone's Effects on Operant Responding Depend Upon Level of Deprivation

J. M. RUDSKI, C. J. BILLINGTON AND A. S. LEVINE[1]

Research and Medicine Service, Veterans Administration Medical Center, Minneapolis, MN 55417
Departments of Psychiatry, Food Science & Nutrition, Medicine, Surgery and Medicinal Chemistry, University of Minnesota, Minneapolis and St. Paul, MN

Received 10 December 1993

RUDSKI, J. M., C. J. BILLINGTON AND A. S. LEVINE. *Naloxone's effects on operant responding depend upon level of deprivation.* PHARMACOL BIOCHEM BEHAV 49(2) 377–383, 1994.—Naloxone's effects on initiation, maintenance, and maximal response effort to acquire food were examined in rats maintained under different levels of food deprivation. In Experiment 1, naloxone was administered SC to rats responding under an FR 80 (first pellet) FR 3 (subsequent pellets) reinforcement schedule. Naloxone did not increase time to acquire the first pellet. Naloxone's suppression of subsequent intake and lowest effective dose were inversely related to level of deprivation. In Experiment 2, rats responded for food under a Progressive Ratio 2 reinforcement schedule. Breakpoint was lowered only when rats were maintained with free access to food. Decreases in response and running rate were inversely related to deprivation level. Results are consistent with the hypothesis that opioids are involved in the maintenance but not the initiation of feeding.

Naloxone Opiates Feeding Operant reinforcement

MANY reports indicate that endogenous opioids influence short-term food intake. Agonists of the mu, kappa, and delta receptors increase free feeding in many species (17). Naloxone, a primarily mu receptor antagonist reliably decreases free-feeding, as well as feeding induced by deprivation, tail pinch, availability of palatable food, benzodiazepines, clonidine, neuropeptide Y, 2-deoxyglucose, or electrical brain stimulation, across many species (6,17). Similarly, naloxone has been shown to decrease other consummatory behaviors (4,5,24). However, when administered to animals responding for food in operant chambers, naloxone has been reported to be insensitive in decreasing responding across many species (10,12, 13,16,19,21,29), unless previously treated with chronic morphine (22). Typically, naloxone-induced decreases in food-maintained operant responding requires doses 10 to 100 times larger than those that suppress free feeding. Such doses are sufficiently high as to raise questions regarding opioid specificity of the naloxone effect.

The differential effects of naloxone on intake commonly reported between free-feeding and food-reinforced operant responding may be due to differences between the two assessment procedures rather than an effect specific to the drug. Studies reporting naloxone-induced decreases in food intake use satiated or acutely deprived (i.e., 24–48 h) animals, whereas operant studies reporting no naloxone effect on responding for food use chronically deprived animals (animals maintained at 80–85% of their free-feeding body weights over a period of weeks to months). Opiate-induced changes in food intake are influenced by the deprivation state of animals. Morphine, a mu agonist that increases food intake in satiated rats, decreases intake in food-deprived rats (23). The sensitivity of the morphine effect on food intake to deprivation may be paralleled by naloxone.

This study reexamined naloxone's effects on operant responding in rats maintained under different feeding conditions: chronic deprivation, free access to food, and restricted access with respect to when food was available in home cages. Naloxone has previously been reported to affect maintenance but not initiation of feeding behavior in a runway experiment (i.e., naloxone-decreased food consumption decreased without altering running speed) (14,15). Thus, we decided to use an operant schedule that we believed to be analogous to the runway procedure, requiring substantially more work to initially obtain food than for subsequent consumption. Furthermore, because naloxone has been suggested to produce its anorectic effect by producing early satiation (14), the micro-

[1] Requests for reprints should be addressed to A. S. Levine, Research Service (151), VA Medical Center, Minneapolis, MN 55417.

structure of feeding over the session was examined. Finally, naloxone's effects on motivation to acquire food were examined using a progressive ratio reinforcement schedule.

METHOD

Subjects

Thirty-six experimentally naive male Sprague-Dawley rats (Harlan Sprague-Dawley, Madison WI), starting weights 300-325 g, were housed in conventional individual wire hanging cages with a 12 L : 12 D photoperiod (lights on at 0700 h) in a temperature-controlled vivarium (21-22°C). Tap water was available ad lib, and food availability was dependent upon experimental treatment (see below). Eighteen rats each were used in Experiment 1 and Experiment 2.

Food Availability

In both Experiment 1 and Experiment 2 each rat was examined under all three deprivation levels, with treatment order being block randomized across animals. In the free-access condition, food was available ad lib in hoppers at the front of each rats cage. In the restricted-access condition, rats were maintained at 100% of their body weights, but rather than having food available in their hoppers, their daily ration of food (22 g) was placed at the base of each rats cage at approximately 1500 h. In the chronically deprived condition, rats were reduced to 90% of their free-feeding weights over 3 days and maintained at their weight by limiting their daily intake to 18-19 g food/day. Rats were given 7-10 days to adapt to each food availability condition before drugs were administered, at which time responding did not show systematic change from session to session. Operant sessions were run daily during each period of adaptation.

Apparatus

Experimental sessions were conducted in six commercially available small animal operant chambers (Model E10-10TC, Coulbourn Instruments, Inc.). Each chamber was enclosed in an isolation cubicle (Model E10-20, Coulbourn Instruments, Inc.) to attenuate outside noise. Chambers were equipped with two operant levers on opposite sides of the front panel of the chamber. The left lever was used exclusively throughout the study. The house light, located in a top central position, was illuminated throughout the experimental sessions. Dustless precision pellets (45 mg) (Bioserv Holton Industries, Frenchtown, NJ) could be delivered to a pellet trough between the levers. When a pellet was delivered, a 4 W light above the pellet trough was illuminated for 1 s. A Zeos computer, immediately adjacent to the chambers, controlled experimental conditions and recorded data.

Procedure

In Experiment 1, rats were reduced to 85% of their free-feeding weights over 5 days and trained to press the left lever under an FR 80 reinforcement schedule for the first pellet, FR 3 for each subsequent pellet. Following 10-14 days of training rats were assigned to their initial food access conditions. This reinforcement schedule allows for examination of naloxone's effects on both the initiation (FR 80 component) and maintenance (FR 3) of food intake. Sessions lasted 1 h. Naloxone (0, 0.3, 1.0, 3.0, 10.0 mg/kg) was injected SC 20 min before sessions, and the order of doses was randomized. The time to acquire the first pellet and total number of pellets consumed over the session were recorded. Rats not responding during the session were assigned an acquisition latency of 3600 s. An overall two-factor RMANOVA (food availability condition × naloxone dose) was employed to analyze pellet acquisition time and number of pellets consumed. Separate RMANOVAs at each feeding condition determined dose effects, and post hoc analyses of acquisition time and amount consumed were performed using the Dunnet's multiple comparison test. Between-group differences comparing naloxone's effects on feeding condition were determined with a RMANOVA following conversion of each rats' individual data into a percent of the mean control for each deprivation condition, and post hoc comparisons were done using Dunn's multiple comparison test.

In order to examine responding over the session, the number of pellets consumed after the first reinforcer delivery was accumulated into 10-min bins. If latency to acquire the first pellet precluded access to all bins, they were left empty and not included in the data analysis (e.g., with session length being 60 min, a rat who required 30 min to complete the FR 80 only had data entered in the first three 10-min bins, and the remaining bins remained empty for that subject). An overall RMANOVA could not be performed due to missing cells in the free-access condition, so separate RMANOVAs were utilized to analyze intake in each bin under each food availability condition. Post hoc effects were assessed using Dunnet's multiple comparisons test. Distribution of food intake throughout the session was examined by converting intake in each bin into a percent of the mean total pellets consumed and then analyzed with a RMANOVA. Post hoc effects were assessed using Dunn's multiple comparisons test.

In Experiment 2, naloxone's effects were examined using a progressive ratio 2 (PR 2) reinforcement schedule. Under such a schedule, a rat must emit an additional two responses for each subsequent reinforcer (e.g., one press for the first pellet, three presses for the second, five for the third, and so on). The last ratio completed is termed the breakpoint and is used to assess how much work the rat will emit to acquire the reinforcer, and is an alternate measurement of motivation than number of pellets consumed. In the current study, breakpoint was defined as the last ratio completed prior to 10 min elapsing without completing the current ratio. Naloxone (0, 0.3, 1.0, 3.0, 10.0 mg/kg) was delivered SC 20 min before sessions. The order of doses and food availability condition was randomized. Breakpoint, response rate (# responses/min over the entire session), and running rate (which subtracts the postreinforcement pause from response rate, giving the rate of responding while the rat is actually engaged in lever pressing) were recorded. Statistics performed were similar to those assessing number of pellets consumed and acquisition time in Experiment 1.

In order to assess the effects of feeding condition on the various dependent measures in Experiments 1 and 2, data obtained from the saline dose under each condition were compared with a RMANOVA, and post hoc comparisons were done using Dunn's multiple comparison test.

Sessions occurred between 0900-1300 h (2 to 6 h following lights on).

RESULTS

Effect of Intersession Food Availability on Responding

Type of feeding condition produced pronounced differences in food intake and latency to begin eating (Table 1).

TABLE 1

DEPENDENT MEASURES (MEAN ± SEM) FOR EACH FOOD AVAILABILITY CONDITION FOLLOWING SALINE ADMINISTRATION

	Feeding Condition		
	Free Access	Restricted Access	Chronic Deprivation
FR 80- FR 3			
Number of pellets	56.5 ± 12.0	203.1 ± 18.0	300.6 ± 20.4
Acquisition time (s)	1574.5 ± 393.4	296.7 ± 77.4	114.1 ± 16.1
Progressive Ratio 2			
Breakpoint	31.5 ± 2.9	52.4 ± 4.0	100.2 ± 9.6
Response rate (#/min)	19.1 ± 0.3	38.7 ± 4.2	71.0 ± 7.7
Running rate (#/min)	64.2 ± 11.0	83.52 ± 7.1	104.6 ± 11.1

Restricted access produced significantly ($p < 0.05$) lower values for all measures relative to chronic deprivation, and free access produced significantly lower values than did restricted access (Dunn's multiple comparisons).

Total intake following saline administration was greatest when rats were chronically deprived, followed in order by the restricted- and free-access conditions, $F(2, 34) = 53.5$, $p < 0.01$. Latency to begin eating was longest under the free-access condition and shortest under chronic deprivation, $F(2, 34) = 12.33$, $p < 0.01$. These treatments also produced different patterns of feeding across sessions. Feeding was more distributed throughout the session as deprivation conditions became more severe, $F(2, 16) = 4.69$, $p < 0.05$ (see Fig. 4 below).

Responding under the PR 2 reinforcement schedule was also affected by food availability. Breakpoints following saline administration were highest under chronic deprivation conditions and lowest under free feeding, $F(2, 32) = 49.2$, $p < 0.05$. Response and running rates showed a similar pattern, $F(2, 32) = 40.10$, $p < 0.01$, and $F(2, 32) = 7.50$, $p < 0.05$, respectively. One rat frequently did not reach a breakpoint after 2-1/2 h of responding and his data was excluded from the analysis (as naloxone's anorectic effect is short lived).

Naloxone's Effects on the Initiation and Maintenance of Responding for Food

Naloxone decreased the number of pellets consumed over the session, $F(5, 85) = 15.15$, $p < 0.01$. Significant (i.e., $p < 0.05$) main effects for naloxone were obtained for all three food availability conditions, $F(5, 85) = 4.147$, when maintained with free access; $F(5, 85) = 14.90$, with restricted access; $F(5, 85) = 4.05$, with chronic deprivation). The magnitude of the percent decrease depended upon feeding condition, $F(2, 34) = 29.27$, $p < 0.05$ (Fig. 1), with the lowest effective dose and greatest degree of suppression occurring when rats had free access to food.

Whereas overall time to acquire the first pellet was increased by naloxone, $F(5, 85) = 3.25$, $p < 0.01$, this effect was weak as dose-effect analyses at each food-availability condition revealed no significant differences, $F(5, 85) = 2.26$, $p = 0.56$; $F(5, 85) = 0.90$, $p > 0.05$; $F(5, 85) = 0.11$, $p > 0.05$, for free access, restricted access, and chronic deprivation, respectively. Furthermore, the percent decrease was not statistically different between the different food availability conditions, $F(2, 34) = 1.34$, $p > 0.05$ (Fig. 2).

Although naloxone did not alter acquisition latency in food-restricted and in chronically deprived rats, naloxone did produce immediate decreases in amount of consumption upon acquisition of the first pellet. Decreases relative to saline were observed over the first 10 min following completion of the initial ratio in the free-access condition, $F(5, 10) = 3.88$, $p < 0.05$, restricted-access condition, $F(5, 75) = 14.20$, $p < 0.05$, and chronic deprivation condition, $F(5, 85) = 16.21$, $p < 0.05$ (Fig. 3). Similar decreases were present over the next 10 min in each condition, $F(5, 10) = 3.78$; $F(5, 75) = 10.87$; $F(5, 85) = 7.54$, $p < 0.05$ for free access, restricted access, and chronically deprived, respectively. Due to increasing variability and empty cells resulting in decreased statistical power, significant decreases over any subsequent 10-min bins were not observed with the exception of the third bin in the restricted access condition, $F(5, 70) = 3.45$, $p < 0.05$. As a result of high naloxone doses (1.0 to 10.0 mg/kg) eliminating almost all responding when rats were maintained with free access to food, most animals were not included in the RMANOVA in that particular deprivation condition (due to empty data cells). This resulted in a substantial decrease in

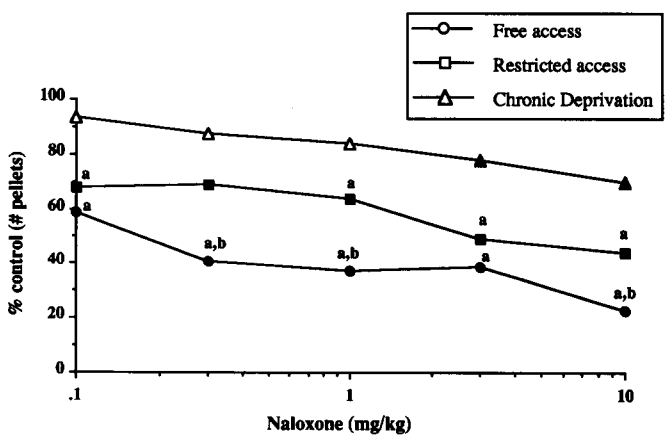

FIG. 1. Experiment 1. Naloxone's effect on total number of pellets (mean percent of control) presented under the FR 80 (first pellet) FR 3 (subsequent pellets) reinforcement schedule for each feeding condition. Filled data points indicate significantly different from saline, 'a' significantly different from the chronic deprivation condition, 'b' significantly different from the restricted access condition.

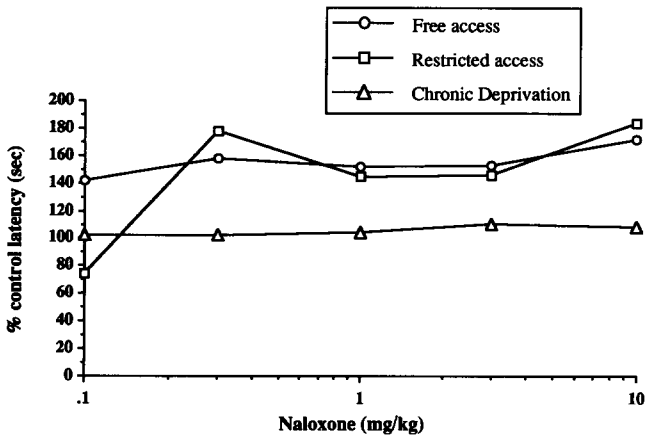

FIG. 2. Experiment 1. Naloxone's effect on mean percent of control time to complete the initial ratio (i.e., FR 80) from the start of the session for each feeding condition.

statistical power and prevented significant posthoc effects following the lower doses. Analysis with paired *t*-tests demonstrated a significant decrease in food intake following every naloxone dose.

Chronic deprivation resulted in greater distribution of food intake throughout the session than did the free- or restricted-access conditions, in which most of the intake occurred within the first two 10-min bins (see above) (Fig. 4). Naloxone did not systematically alter the pattern of eating in any food availability condition, $F(5, 60) = 0.11$; $F(5, 75) = 0.18$; $F(5, 85) = 0.01, p < 0.05$ for free access, restricted access, and chronically deprived, respectively.

Naloxone's Effects on Responding Under a PR 2 Reinforcement Schedule

Naloxone decreased overall breakpoint, $F(5, 80) = 5.79$, $p < 0.01$. Significant (i.e., $p < 0.05$) main effects for naloxone were obtained when rats were maintained with free-access to food, $F(5, 80) = 9.87$, $p < 0.05$, and approached significance when maintained with restricted access, $F(5, 80) = 2.11$, $p = 0.07$. A small but statistically reliable increase in breakpoint was produced by naloxone when rats were chronically deprived, $F(5, 80) = 4.21$, $p < 0.05$. Naloxone-induced percent decreases were greatest when rats had free access to food, $F(2, 32) = 5.23$, $p < 0.05$ (Fig. 5).

Naloxone decreased both overall response and running rate, $F(5, 80) = 10.16$, $p < 0.01$, and $F(5, 80) = 4.33$, $p < 0.01$, respectively. Significant (i.e., $p < 0.05$) main effects for naloxone on response rate were obtained under all food availability conditions, $F(5, 80) = 5.11$; $F(5, 80) = 5.18$; $F(5, 80) = 3.02, p < 0.05$ for free access, restricted access, and chronically deprived, respectively. Main effects on running rate were also observed when rats were maintained with free access, $F(5, 80) = 3.59$, $p < 0.05$, or restricted access, $F(5, 80) = 2.65$, $p < 0.05$, but not when chronically deprived, $F(5, 80) = 0.89$, $p > 0.05$. Although percent decreases in response rate were not significantly different under the three food availability conditions, $F(2, 32) = 1.80$, $p > 0.05$, degree of percent suppression of running rate was affected by food availability, $F(2, 32) = 15.91$, $p < 0.05$. Running rate decreases were produced by lower naloxone doses under the free-access condition (Fig. 6).

DISCUSSION

The present investigation examined naloxone's effects on the initiation, maintenance, and motivational aspects of feeding behavior. Previous research has suggested that naloxone does not readily interfere with food-reinforced operant responding (10,12,13,16,19,21,29). From the above experiments, it is apparent that naloxone's effects depend upon the deprivation state of the animal.

Unlike previous studies reporting little if any effect of naloxone on food-reinforced operant responding, the current study indicates that naloxone can decrease such responding when subjects are not deprived or maintained under mild deprivation conditions. Studies in which food-maintained responding is unchanged by naloxone typically use chronically deprived animals, the one condition in which naloxone was relatively ineffective in the current study. When nondeprived animals responding for reinforcers other than food are given naloxone, decreases in consumption at doses similar to those observed in this study are reported (24).

Previous interactions between level of deprivation and opioid effects have been reported. Sanger and McCarthy (23) found that morphine decreased food intake in food-deprived animals at similar doses that produced increases in satiated ones. Furthermore, interactions between opiates, food, and level of deprivation may have a neurological basis. Lesions of the tegmental pedunculopontine nucleus blocked both morphine and food-conditioned place preferences in drug-naive

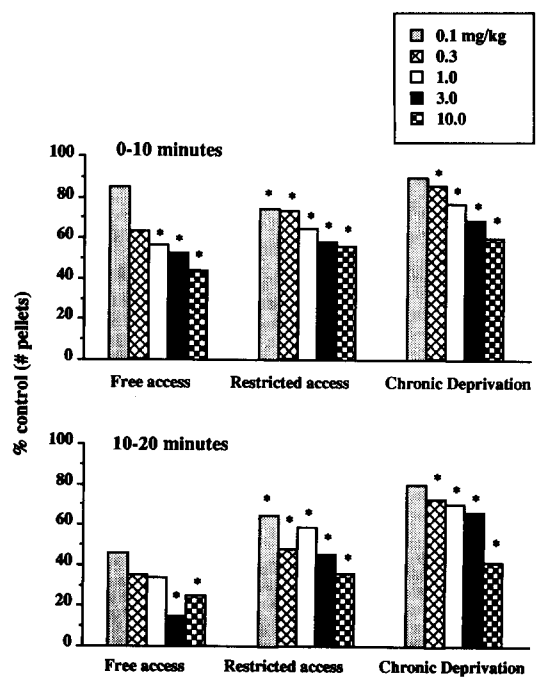

FIG. 3. Experiment 1. Naloxone's effect on total number of pellets (mean percent of control) acquired in the first and second 10-min bins presented under the FR 3 contingency for each feeding condition. *$p < 0.05$ compared to saline.

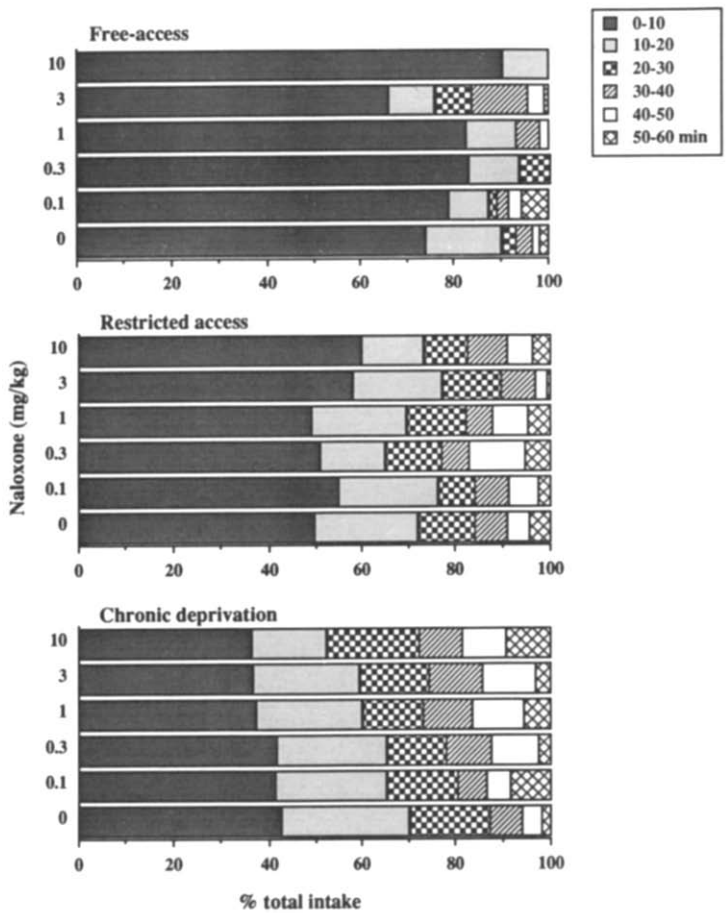

FIG. 4. Naloxone's effect on pattern of eating (i.e., percent of the mean total intake occurring in each 10-min bin) within sessions for each feeding condition.

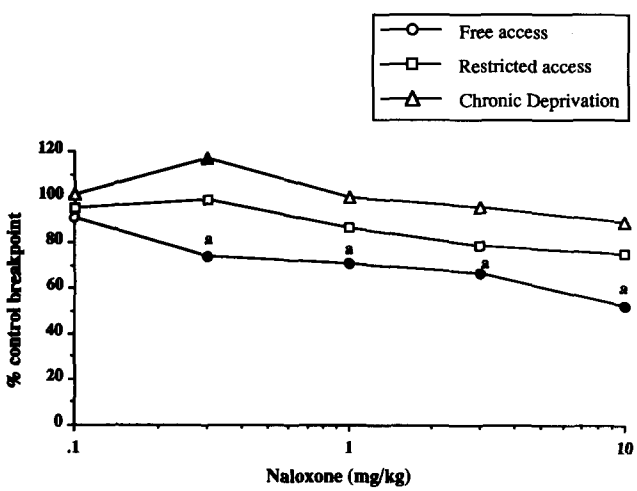

FIG. 5. Experiment 2. The effect of naloxone and feeding condition on breakpoint (mean percent of control) obtained using a PR 2 reinforcement schedule. Filled data points indicate significantly different from saline, 'a' significantly different from the chronic deprivation condition, 'b' significantly different from the restricted access condition.

and food-satiated rats, respectively, but failed to block morphine and food-conditioned place preferences in morphine-dependent and food-deprived rats (2). This suggests separate mechanisms subserving deprivation- and nondeprivation-induced motivation.

The results of the current study agree with previous studies in which naloxone decreases consumption of a wide variety of reinforcers. However, contrary to previous studies reporting naloxone-induced decreases of home cage free feeding in deprivation-induced feeding (6,17), naloxone in the current study proved relatively ineffective in decreasing intake in chronically deprived rats. Perhaps the deprivation state in the current study (i.e., chronic deprivation) was not analogous to the deprivation states used in previous experiments (i.e., acute deprivation). Studies reporting naloxone-induced decreases typically use animals acutely deprived for 24–48 h rather than their being chronically deprived over several weeks. Chronic and acute deprivation produce different types of hunger states, each with unique physiological changes. Most evidence suggests that opioids are more involved in the short-term maintenance of feeding. One study that examined naloxone's effects in chronically deprived rats did not observed significant decreases in free feeding following a dose as high as 10.0 mg/kg (18). It is likely that naloxone would have less of an effect in modifying intake induced by chronic deprivation.

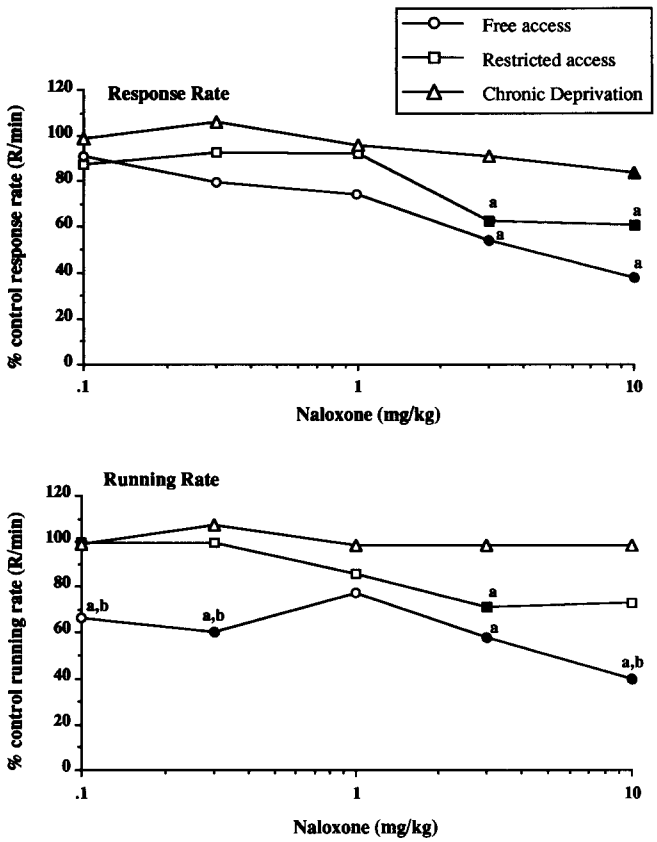

FIG. 6. Experiment 2. The effect of naloxone and feeding condition on response and running rate (mean percent of control) under a PR 2 reinforcement schedule. Filled data points indicate significantly different from saline, 'a' significantly different from the chronic deprivation condition, 'b' significantly different from the restricted access condition.

In using a reinforcement schedule with a high ratio value for the initial pellet and a low ratio value for subsequent pellets, Experiment 1 examined both initiation and maintenance of food intake in an operant chamber situation analogous to a runway maze. Initiation was not affected by naloxone (although when rats were maintained with free access to food the effect closely approached statistical significance). Naloxone interfered with maintenance of feeding in all food-availability conditions, with the greatest decreases in total food intake occurring when rats were maintained under free-access conditions, followed in order by restricted access and chronic deprivation. By using a progressive ratio reinforcement schedule, Experiment 2 examined how much work an animal would emit to acquire food (i.e., motivation). Once again, naloxone-induced changes were affected by deprivation level. Breakpoint, response, and running rate decreases followed administration of lower doses and were of greater magnitude when rats were maintained under free-access conditions.

Naloxone has been proposed to have less of an effect on initiation than on maintenance of consummatory behavior. For example, naloxone has no effects on speed of traversing a runway to acquire food, yet decreases the amount of food consumed once rats are in the goal box (14). Similarly, Cooper and Holtzman (5) found naloxone-induced decreases in drinking duration without any effect on latency to begin to drink. Data from the current study support this suggestion. Naloxone affected initiation to a much lesser extent than maintenance as inferred from the FR 80 FR 3 reinforcement schedule. Naloxone-induced changes on acquisition time of the first pellet approached statistical significance only in the free-access condition, whereas naloxone administration decreased number of pellets consumed in all conditions.

It has been suggested that naloxone interferes with maintenance of consummatory behavior by producing early satiation (14). Early satiation would be manifested by comparable rates of initial food intake, followed by a dose-related termination of feeding earlier in the session. Results from the current study are not in agreement with this prediction. Intake was suppressed by naloxone within the first 10 min of the maintenance phase of the sessions (indeed, analysis of intake in the first 5 min yielded identical results). Thus, such immediate decreases are unlikely to be due to satiety.

Further evidence against a satiety mechanism underlying naloxone's anorectic effects can be inferred from discrepancies reported between naloxone's and cholecystokinin's (CCK) operant effects. CCK is a peptide that is widely believed to decrease feeding by producing satiety (20,25). Whereas naloxone was ineffective in decreasing responding or intake in food-deprived animals in the current and previous studies, CCK decreases FR responding and food intake in deprived rats (1,26,27). This differential effect between the agents suggests that they might be decreasing intake through different mechanisms.

The opioid system has been hypothesized to alter consummatory behavior by influencing rewarding properties of food, as suggested by interactions between palatability and opioid activity or effects. Consumption of palatable food alters opioid binding and beta-endorphin levels in rats hypothalamus (8), and ingestion of palatable foods results in naloxone-reversible increases in nociceptive thresholds (3). Similarly, opiate administration increases intake of preferred foods to a greater extent than nonpreferred one (11). Opioid antagonists show a similar differential sensitivity, more potently decreasing preferred food when presented concurrently with nonpreferred food (6). Furthermore, the reported pleasantness of sweet foods is decreased by opioid antagonists in humans (9,28). Decreased consumption following naloxone is not limited to food. Decreased consumption of ethanol, saccharine, glucose, and water have also been reported (24). Finally, naloxone decreases food intake in sham-fed rats, suggesting an effect on the orosensory qualities of the food completely independent of any satiation mechanism (15). The decreased intakes observed following naloxone in the current study may have been due to such an alteration of the rewarding properties of the food. The 45 mg pellets presented as reinforcers had a high sucrose concentration, and we have found that rats find them more palatable than regular chow (unpublished observation). One would expect that the role of a food's orosensory qualities is inversely related to deprivation level: the hungrier the rat is, the less likely it is that food intake will be changed by alterations of the rewarding or orosensory qualities of food. That naloxone-induced decreases in food-maintained responding (and, hence, food intake) in the current study were greatest when the rats were least hungry supports these suggestions. However, it is also possible that responding in the free-access condition represented residue of the experience of previous deprivation rather than being palatability derived.

In sum, naloxone's effects on operant responding under both fixed- and progressive-ratio schedules depended to a

large extent upon deprivation state. Furthermore, the current study supported previous findings suggesting a greater role of the opioid system in the maintenance of food intake than in its initiation.

ACKNOWLEDGEMENTS

This work was supported by the Department of Veterans Affairs, National Institute of Drug Abuse DA 03999, and National Institute of Aging AG00198.

REFERENCES

1. Babcock, A. M.; Livosky, M.; Avery, D. D. Cholecystokinin and bombesin suppress operant responding for food reward. Pharmacol. Biochem. Behav. 22:893–895; 1985.
2. Bechara, A.; van der Kooy, D. A single brain stem substrate mediates the motivational effects of both opiates and food in nondeprived but not in deprived rats. Behav. Neurosci. 106:351–363; 1992.
3. Bergmann, F.; Lieblich, I.; Cohen, E.; Ganchrow, J. R. Influence of intake of sweet solutions on the analgesic effect of a low dose of morphine in randomly bred rats. Behav. Neural Biol. 44: 347–353; 1985.
4. Cooper, S. J. Effects of opioid agonists and antagonists on fluid intake and saccharine choice in the rat. Neuropharmacology 22: 323–328; 1983.
5. Cooper, S. J.; Holtzman, S. G. Patterns of drinking in the rat following the administration of opiate antagonists. Pharmacol. Biochem. Behav. 19:505–511; 1983.
6. 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 Ltd; 1988.
7. Drenowski, A.; Krahn, D. D.; Demitrack, A.; Nairn, K.; Gosnell, B. A. Taste responses and preferences for sweet high-fat foods: Evidence for opioid involvement. Physiol. Behav. 51:371–379; 1992.
8. Dum, J.; Gramsch, C.; Herz, A. Activation of hypothalamic beta-endorphin pools by reward induced by highly palatible food. Pharmacol. Biochem. Behav. 18:443–447; 1983.
9. Fantino, M.; Hosette, J.; Apfelbaum, M. An opioid antagonist, naltrexone, reduced preference for sucrose in humans. Am. J. Physiol. 251:R91–R96; 1986.
10. France, C. P.; Woods, J. H. Antagonistic and rate-suppressant effects of opioid antagonists in the pigeon. J. Pharmacol. Exp. Ther. 235:442–447; 1985.
11. 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.
12. Harris, R. A. Interactions between narcotic agonists, partial agonists and antagonists evaluated by schedule-controlled behavior. JPET 213:497–503; 1980.
13. Katz, J. L. Interactions of clonidine and naloxone on schedule-controlled behavior in opioid-naive mice. Psychopharmacology (Berlin) 98:445–447; 1989.
14. Kirkham, T. C.; Blundell, J. E. Effect of naloxone and naltrexone on the development of satiation measured in the runway: Comparisons with *d*-amphetamine and *d*-fenfluramine. Pharmacol. Biochem. Behav. 25:123–128; 1986.
15. Kirkham, T. C.; Cooper, S. J. Attenuation of sham-feeding by naloxone is stereospecific: Evidence for opioid mediation of orosensory reward. Physiol. Behav. 43:845–847; 1988.
16. Leander, J. D. Behavioral effects of phenylpiperidine narcotic antagonists. Pharmacol. Biochem. Behav. 15:65–70; 1981.
17. Levine, A. S.; Billington, C. J. Opioids. Are they regulators of feeding? Ann. NY Acad. Sci. 575:209–219; 1989.
18. Levine, A. S.; Morley, J. E.; Raij, L. Opiates and the anorexia of uremia. Physiol. Behav. 37:835–838; 1986.
19. McMillan, D. E. Effects of narcotics and narcotic antagonists on operant behavior. Adv. Biochem. Pharmacol. 8:345–359; 1973.
20. Morley, J. E.; Levine, A. S.; Gosnell, B. A.; Mitchell, J. E.; Krahn, D. D.; Nizielski, S. E. Peptides and feeding. Peptides 6: 181–192; 1985.
21. Oliveto, A. H.; Dykstra, L. A. Diprenorphine and naloxone in squirrel monkeys with enhanced sensitivity to opioid antagonists. Psychopharmacology (Berlin) 95:339–343; 1988.
22. Picker. M. J.; Yarbrough, J. Cross-tolerance and enhanced sensitivity to the response-rate decreasing effects of opioids with varying degrees of efficacy at the mu receptor. Psychopharmacology (Berlin) 105:459–466; 1991.
23. Sanger, D. J.; McCarthy, P. S. Differential effects of morphine on food and water intake in food deprived and freely feeding rats. Psychopharmacology (Berlin) 72:103–106; 1980.
24. Schwarz-Stevens, K. S.; Files, F. J.; Samson, H. H. Effects of morphine and naloxone on ethanol- and sucrose-reinforced responding in nondeprived rats. Alcohol.: Clin. Exp. Res. 16:822–832; 1992.
25. Smith, G. P.; Gibbs, J. Cholecystokinin and satiety in rats and rhesus monkeys. Am. J. Clin. Nutr. 30:758–761; 1981.
26. Wilson, M. C.; Denson, D.; Bedford, J. A.; Hunsinger, R. N. Pharmacological manipulation of sincalide (CCK-8)-induced suppression of feeding. Peptides 4:351–357; 1983.
27. Winsauer, P. J.; Riley, A. L. Cholecystokinin potentiates the rate-decreasing effects of morphine on schedule-controlled behavior in rats. Pharmacol. Biochem. Behav. 30:569–575; 1988.
28. Yeomans, M. R.; Wright, P. Lower pleasantness of palatable foods in nalmafene-treated human volunteers. Appetite 16:249–259; 1991.
29. Young, A. M.; Woods, J. H. Limitations on the antagonistic actions of opioid antagonists. Fed. Proc. 41:2333–2338; 1982.