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Individual Differences in the Feeding and Locomotor Stimulatory Effects of Acute and Repeated Morphine Treatments

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SILLS, T. L. AND F. J. VACCARINO. *Individual differences in the feeding and locomotor stimulatory effects of acute and repeated morphine treatments.* PHARMACOL BIOCHEM BEHAV **60**(1) 293–303, 1998.—Rats with high propensity to ingest sugar (HIGH) show increased responsiveness to amphetamine treatments than rats with low propensity to ingest sugar (LOW). Intrinsic variation in the functioning of the mesolimbic dopamine system has been suggested to account for these individual differences. Morphine has stimulatory effects on feeding and locomotion that are in part mediated by the mesolimbic dopamine system. The present study therefore examined whether LOW and HIGH rats would exhibit differences in the feeding and locomotor stimulating effects of morphine. Morphine (1, 2, and 4 mg/kg) significantly stimulated the intake of chow and sugar in LOW rats without affecting food consumption in HIGH rats. Further, it was found that both groups of rats did most of their feeding in the first 20 min following injection, and that the stimulatory effect of morphine in LOW rats was restricted to the first hour of the 3-h test session. Repeated morphine (2 mg/kg) stimulated sugar intake in LOW but not HIGH rats, and there was no evidence of increased intake across injections. Acute administration of 5.0 mg/kg, but not 2.0 mg/kg, of morphine produced higher levels of locomotor activity in LOW rats compared to HIGH rats; repeated treatment with 5.0 mg/kg morphine produced a sensitized locomotor response in both LOW and HIGH rats. These results indicate that LOW rats exhibit increased responsiveness to the locomotor and feeding stimulatory effects of morphine compared to HIGH rats. One implication arising from these findings is that LOW and HIGH rats may be distinguished by differences in opiatergic function, as well as by differences in dopaminergic function. © 1998 Elsevier Science Inc.

Locomotion Sensitization Rats Food intake Sugar Opiate

CONSIDERABLE evidence indicates that rats exhibit individual differences in behaviors mediated by the mesocorticolimbic dopamine (DA) pathway (5,6,9,11–17,25–27,29,31–33). Animals that exhibit high novelty-induced locomotor behavior show a greater locomotor response to amphetamine and cocaine, and more readily self-administer amphetamine than animals that exhibit low novelty-induced locomotor activity (16,25). Further, rats expressing high levels of novelty-induced activity exhibit higher DA release in the nucleus accumbens (Acb) than low responding animals under baseline and cocaine-stimulated conditions (12), as well as in response to a novel environment (28).

Recent evidence indicates that rats exhibit significant interindividual variation in their consumption of sugar and in their feeding and locomotor response to amphetamine treatments. Rats with low baseline sugar intake (LOW) show an increase in sugar consumption when administered low doses of amphetamine (29,31), an effect that is blocked by intra-Acb administration of the DA receptor block α-flupenthixol. Rats with high baseline sugar intake (HIGH), on the other hand, show a decrease in sugar intake at the same doses (29,31). When locomotor activity is measured, HIGH rats show a greater locomotor response to acute and repeated amphetamine treatments than LOW rats, indicative of a higher level of Acb-DA activity (32). Indeed, HIGH rats exhibit higher levels of Acb-DA overflow than LOW rats following the acute administration of amphetamine (30).

Morphine has stimulatory effects on food intake and locomotor activity that are in part mediated by its actions in the mesolimbic DA system (2,8,18,21,23,24). It has been reported

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that animals exhibit individual differences in their response to the psychoactive properties of morphine, and that intrinsic variability in the functioning of the mesolimbic DA system underlies these differences. Thus, rats with high novelty-induced locomotor activity show higher levels of morphine-induced locomotor activity than low novelty-responding animals (7). Further, animals with high baseline Acb-DA activity have higher rates of morphine self-administration than rats with low DA activity (9).

In light of the fact that there may be a common biological mechanism underlying the expression of individual differences in responsiveness to both amphetamine and morphine, it was of interest to determine the responses of LOW and HIGH rats to morphine treatments. The present study investigated the effects of morphine treatment on feeding and locomotor activity exhibited by LOW and HIGH rats. It is well established that repeated administrations of morphine results in an augmented locomotor response to subsequent morphine treatments (1,4,19,35). Repeated morphine infusions into the Acb has also been shown to produce a sensitization in feeding behavior, and to induce a conditioned feeding response to saline challenge (3). Thus, it was of interest to determine whether LOW and HIGH rats would exhibit differences in their feeding and locomotor responses to either acute or repeated morphine treatments or both.

In one group of LOW and HIGH rats, the effects of systemic morphine treatments (0.0, 1.0, 2.0, 4.0 mg/kg) on the intake of sugar and powdered lab chow were assessed. A second group of LOW and HIGH rats were tested for their consumption of sugar over a 3-h period following treatment with 4.0 mg/kg morphine. A third group of LOW and HIGH rats were tested for their consumption of sugar following repeated administrations of 2.0 mg/kg morphine. In a fourth group of LOW and HIGH rats, the effects of acute and repeated morphine treatments (5.0 mg/kg) on locomotor activity were determined. Finally, a fifth group of LOW and HIGH rats were tested for their locomotor response to an acute administration of 2.0 mg/kg morphine.

METHODS

Subjects

Male Wistar rats (Charles River, Quebec) weighing 280–350 g at the start of the experiment were housed singly in a temperature- and light-controlled environment, with lights on at 0700 h and lights off at 1900 h. Rats had ad lib access to water and standard Purina lab chow pellets throughout the experiment, except where noted.

Food Intake: Acute Morphine Treatments

For 10 days prior to testing, male Wistar rats were habituated to the test diets for 1 h (1500–1600 h) each day; for the remaining 23 h of each day rats had ad lib access to standard Purina lab pellets. The test diets consisted of a choice of granulated sugar and powdered Purina lab chow. Animals were administered saline, 1.0, 2.0, and 4.0 mg/kg morphine in a counterbalanced order; morphine was administered IP in a volume of 1.0 ml/kg. Animals had two drug-free days between each test session. On tests days, animals were removed from their home cages and were injected with the predetermined dose of morphine. After injection, animals were returned to their home cages where two $5 \times 5 \times 3$ cm stainless steel containers of preweighed amounts of sugar and powdered chow had replaced the standard lab diet. Animals were allowed to feed on the test diets for a period of 1 h (1500–1600 h) after which the remaining food (including spillage) was reweighed. Animals were designated LOW ($n = 8$) and HIGH ($n = 8$) rats based on a median split of their intake of sugar in response to saline (0.9%, IP).

A second group of male Wistar rats were given access to sugar for 1 h (1500–1600 h) each day for 7 days; for the remaining 23 h of each day rats had ad lib access to standard Purina lab pellets. These animals were divided into LOW ($n = 8$) and HIGH ($n = 8$) rats as outlined above. Subsequently, these animals were tested for their intake of sugar in response to 4.0 mg/kg morphine over a 3-h test period. For the first hour of the test session, food intake was measured every 20 min, after which the remaining food (including spillage) was reweighed and intake recorded; subsequent to this, the food containers were returned to cages and the animals allowed to feed until the end of the next measurement period. After the first hour, food intake was measured once an hour for 2 h as outlined above.

Food Intake: Repeated Morphine Treatments

For 7 days prior to testing, male Wistar rats were habituated to the test diet of sugar for 1 h (1500–1600 h) each day; for the remaining 23 h of each day rats had ad lib access to standard Purina lab pellets. On day 8, animals were administered saline (0.9%, IP) and their intake of sugar measured for 1 h. Animals were subsequently designated as LOW ($n = 9$) and HIGH ($n = 9$) rats based on a median split of their intake of sugar in response to this saline treatment as previously described (32).

Following the habituation period animals were tested for their consumption of sugar following the repeated administrations of 2.0 mg/kg morphine. Four morphine treatments were preceded and followed by a saline challenge, in an A-B-A design. All drugs were administered IP in a volume of 1.0 ml/kg and animals had two drug-free days between test sessions. Testing was carried out as outlined above with the exception that only sugar was used as the test diet.

Locomotor Activity

On each of 2 days prior to drug testing, LOW ($n = 7$) and HIGH ($n = 7$) rats were removed from their home cages and transported to the room housing the cages with the photocell beams. All rats were placed into the cages and locomotive activity recorded for a period of 3 h (1500–1800 h). On test days, all rats were adapted to the locomotor cages for 1.5 h prior to drug administration; between test days, rats received morphine (5.0 mg/kg, IP) injections in their home cages to minimize the effects of conditioning. All rats were tested for their locomotor response to morphine (5.0 mg/kg, IP) on days 1, 3, 5, 7, and 9, and were administered morphine (5.0 mg/kg, IP) in their home cages on days 2, 4, 6, and 8. A second group of LOW ($n = 5$) and HIGH ($n = 5$) rats were tested for their locomotor response to the acute administration of 2.0 mg/kg morphine.

Apparatus

To measure locomotion, eight photocell beam cages housed in another room were utilized. The cages measured 34×33 cm, with two photocell beams placed 3 cm above the floor, with one beam located 11 cm from the front of the cage, and the other beam located 11 cm from the back of the cage. The floor and back wall of the cages were constructed out of wire

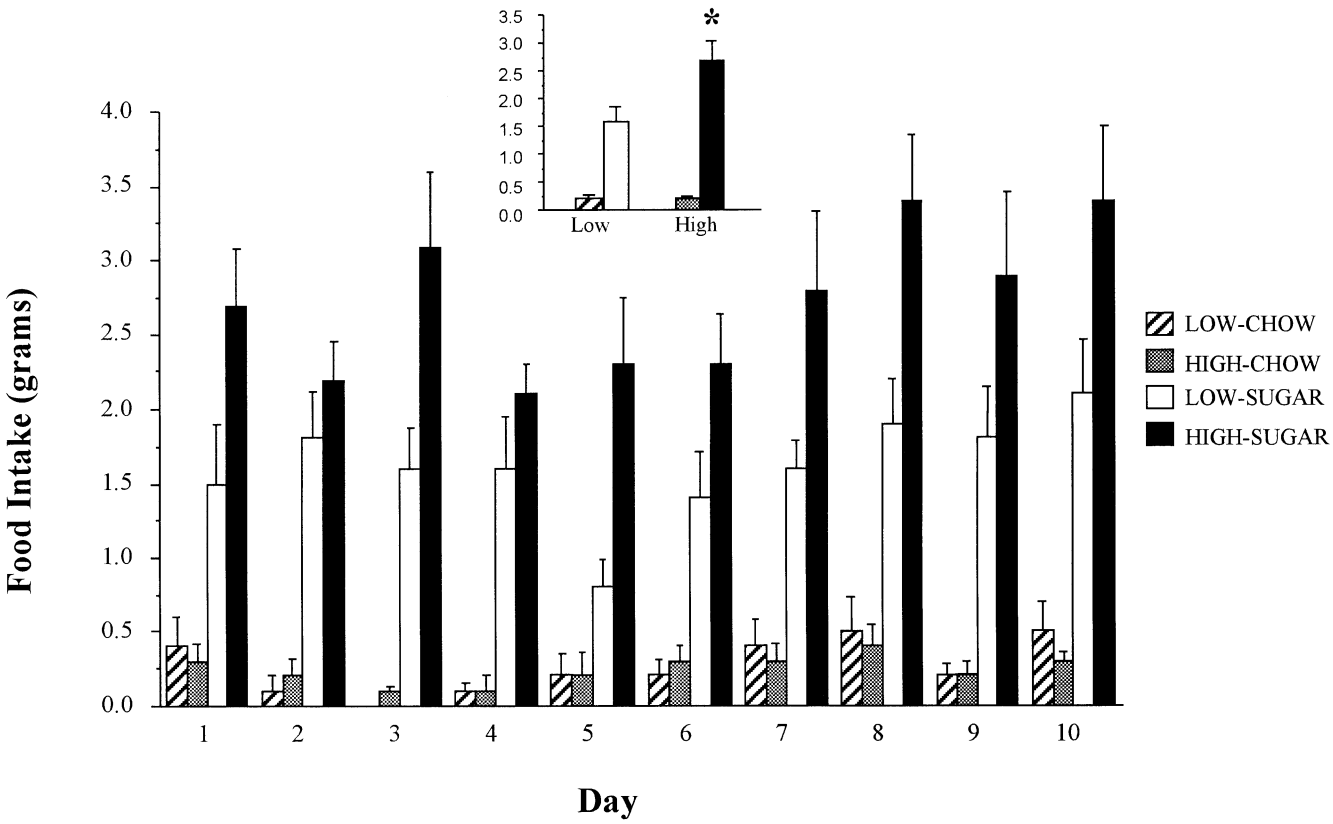

FIG. 1. The average amount of sugar and chow (±SEM) consumed across the 10-day adaptation period by animals designated as LOW and HIGH rats based on a median split of their sugar intake in response to saline treatment. Inset: average daily amount of sugar and chow consumed by LOW and HIGH rats during the adaptation period (*$p < 0.05$ compared to LOW rats).

mesh, with the sides made of metal. The top and front of the cages were constructed out of Plexiglas. The cages were interfaced with a computer located in another room that recorded photocell beam interruptions as counts.

Analyses

Statistical analyses were carried out using Student's *t*-test and Repeated Measures Analysis of Variance (ANOVA), followed by post hoc comparisons using the Least Significant Difference test.

RESULTS

Food Intake: Acute Morphine Treatments

A two-way ANOVA examining the average daily amount of sugar and chow consumed by LOW and HIGH rats across the 10-day adaptation period revealed a significant interaction of group × food, $F(1, 14) = 9.76$, $p < 0.01$. Figure 1 shows that HIGH rats had higher average daily sugar intake than LOW rats but that the two groups did not differ in chow intake. Both groups of animals also consumed more sugar than chow, as indicated by a significant main effect of food, $F(1, 14) = 109.22$, $p < 0.0001$. Figure 2a shows that LOW rats preferred sugar over chow, $F(1, 7) = 18.046$, $p < 0.01$, and morphine treatment produced a significant increase in the intake of both types of food, $F(3, 21) = 5.143$, $p < 0.01$. As shown in Fig. 2b, HIGH rats consumed more sugar than chow across all conditions, $F(1, 7) = 101.384$, $p < 0.0005$, and morphine treatment was without effect on chow and sugar intake, $F < 1.0$.

Figure 3a shows that, as in the first experiment, morphine stimulated sugar consumption in LOW rats over the first hour of the test session, $t(7) = 2.28$, $p < 0.05$. In contrast, morphine did not significantly stimulate the intake of sugar in HIGH rats over the first hour of the test session, $t(7) = 0.93$, $p > 0.05$ (Fig. 3b). Consistent with the first experiment, HIGH rats consumed significantly more sugar than LOW rats in the first hour following saline treatment, $t(14) = 2.49$, $p < 0.05$, and had significantly higher average daily sugar intake levels than LOW rats across the 7-day adaptation period, $t(14) = 2.49$, $p < 0.05$.

To examine the temporal aspects of the feeding response to morphine in LOW and HIGH rats over the first hour of the test session, two-way ANOVAs were carried out examining the amount of sugar consumed following saline or morphine across each of three 20-min intervals. For LOW rats, the ANOVA revealed a significant main effect of interval, $F(2, 14) = 38.59$, $p < 0.05$. Post hoc analyses revealed that LOW rats did most of their feeding over the first 20 min of the first 1-h test period. The ANOVA also showed that the main effect of drug was marginally significant, $F(1, 7) = 5.2$, $p = 0.057$, and the interaction of drug × interval was not significant, $F(2, 14) = 2.04$, $p > 0.05$. For HIGH rats, the ANOVA

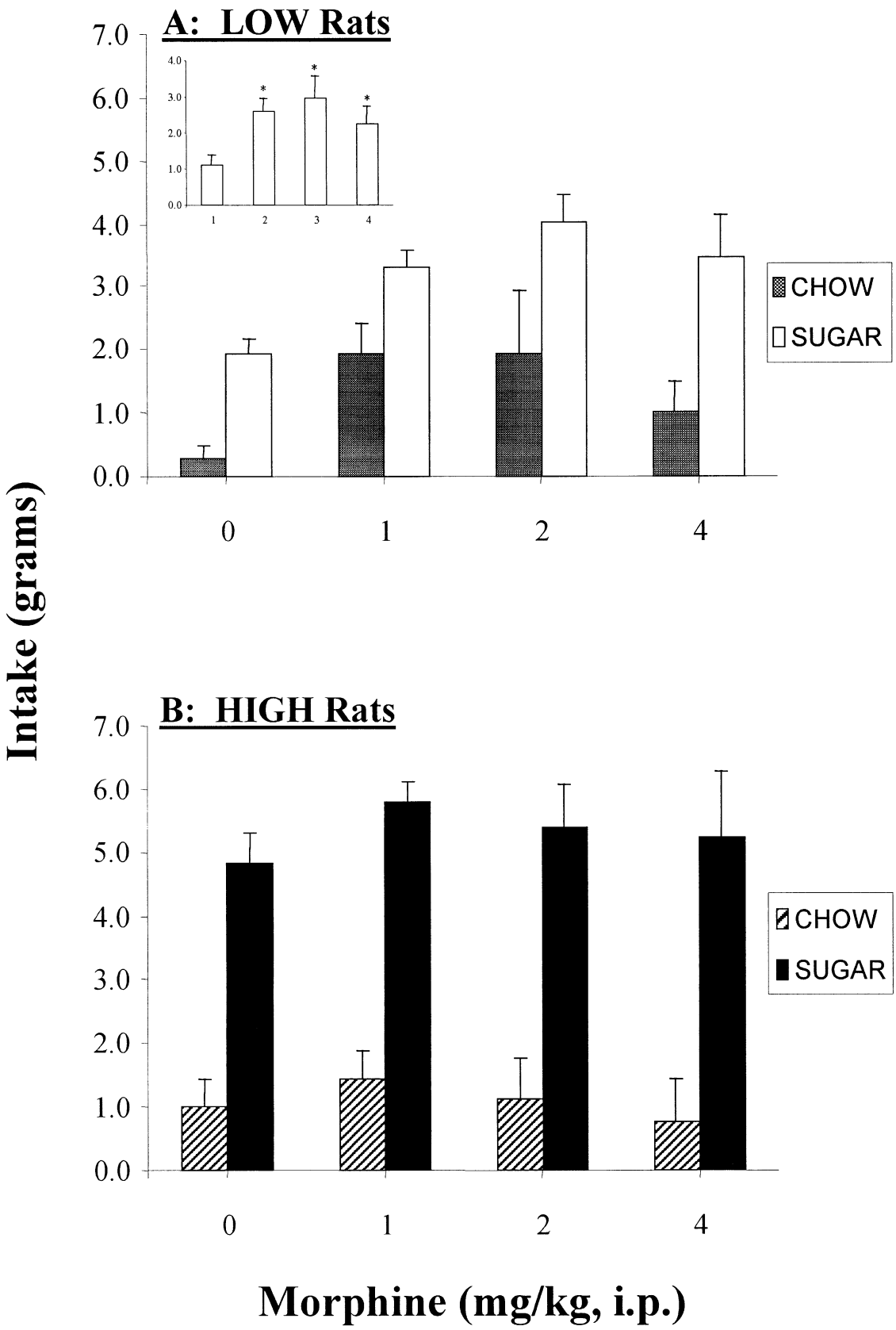

FIG. 2. (A) The average amount of sugar and chow (±SEM) consumed in response to morphine treatment by LOW rats. Inset: total food intake in response to morphine treatment (*$p < 0.05$ compared to 0.0 mg/kg morphine). (B) The average amount of sugar and chow (±SEM) consumed in response to morphine treatment by HIGH rats.

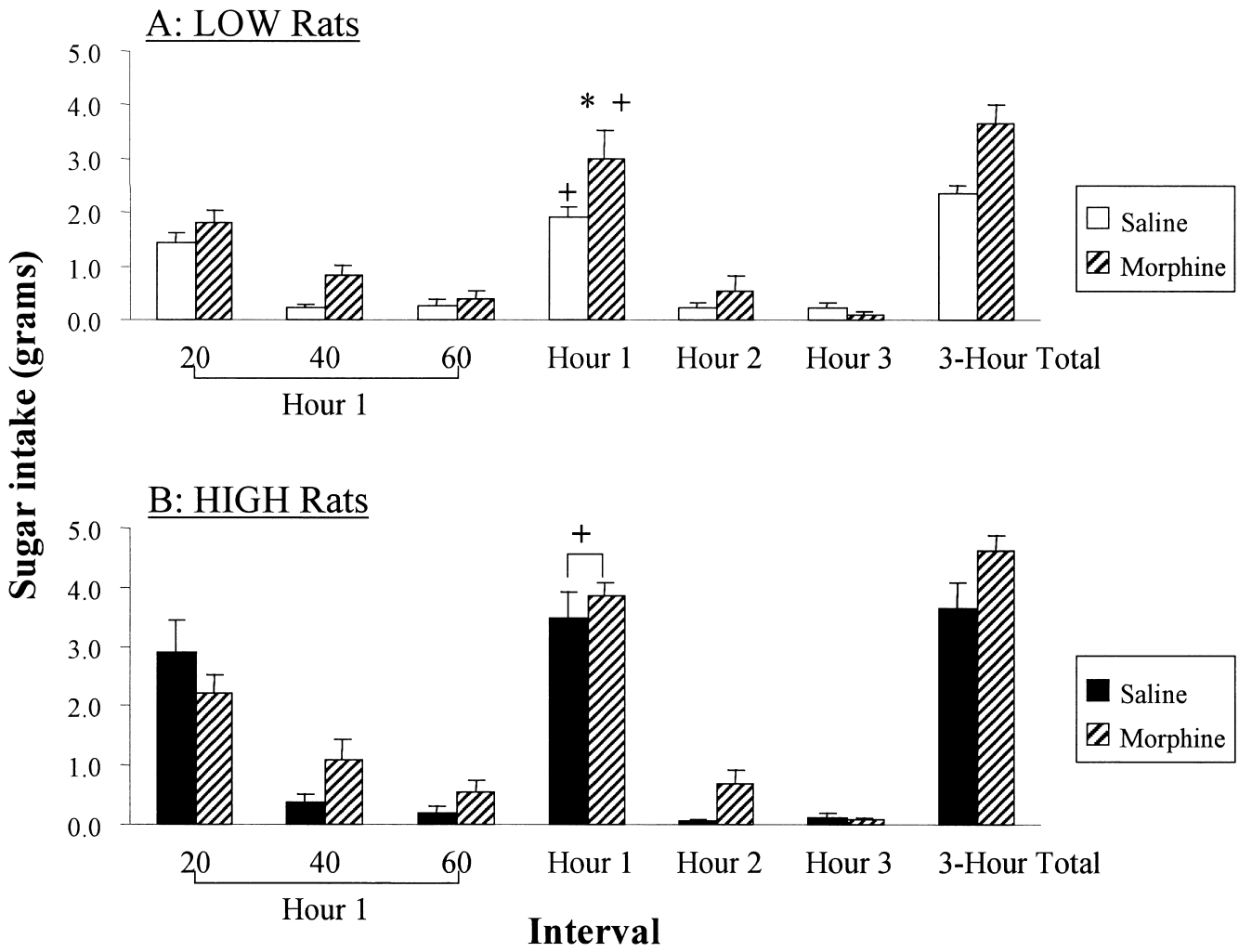

FIG. 3. (A) The average amount of sugar (±SEM) consumed by LOW rats across the 3-h test session in response to 4.0 mg/kg morphine treatment (*$p < 0.05$ compared to 0.0 mg/kg morphine; $^{+}p < 0.05$ compared to hour 2 and hour 3). (B) The average amount of sugar (±SEM) consumed by HIGH rats across the 3-h test session in response to 4.0 mg/kg morphine treatment ($^{+}p < 0.05$ compared to hour 2 and hour 3).

revealed a significant main effect of interval, $F(2, 14) = 18.47$, $p < 0.05$. Again, post hoc analyses revealed that HIGH rats did most of their feeding over the first 20 min of the first 1-h test period. The ANOVA also showed that there was no significant main effect of drug, $F(1, 7) < 1.0$, nor a significant drug × interval interaction, $F(2, 14) = 2.15, p < 0.05$.

To determine whether a delayed feeding facilitatory effect of morphine could be unveiled in HIGH feeders, sugar intake levels were examined across the full 3-h test period. ANOVA revealed a significant main effect of interval, $F(2, 14) = 93.0$, $p < 0.05$. Post hoc analyses revealed that HIGH rats did their majority of feeding in the first hour of the 3-h test session (see Fig. 3b). The ANOVA also showed that there was no significant effect of drug, $F(1, 7) = 4.08$, $p > 0.05$, nor a significant drug × interval interaction, $F(2, 14) = 1.82$, $p > 0.05$. For LOW rats, ANOVA revealed a significant drug × interval interaction, $F(2, 14) = 4.61, p < 0.05$. Post hoc analyses revealed that LOW rats did most of their feeding during the first hour of the 3-h test session, and sugar consumption under morphine was significantly higher than sugar consumption under saline in this period (see Fig. 3a). The ANOVA also showed a significant main effect of intervals, $F(2, 14) = 34.51$, $p < 0.05$, and no significant main effect of drug, $F(1, 7) = 4.66, p > 0.05$.

Food Intake: Repeated Morphine Treatments

HIGH rats exhibited significantly higher average daily sugar intake than LOW rats across the 7-day adaptation period, $t(16) = 1.98$, $p < 0.05$. Figure 4 shows that HIGH rats consumed significantly more sugar than LOW rats following both the first saline injection, $t(16) = 2.28$, and the last saline injection, $t(16) = 3.73$, $p < 0.05$. Figure 4 also shows that in LOW rats, morphine treatment significantly enhanced the intake of sugar, $F(5, 40) = 5.61$, $p < 0.05$. Post hoc analyses revealed that LOW rats consumed significantly more sugar in response to morphine compared to the first saline treatment. Intake under morphine was also significantly higher than intake in response to the second saline treatment, but only on the last day of morphine treatment. There was no evidence of sensitization, as indicated by the fact that there was no difference in sugar intake across the four morphine injections. There was also no evidence of conditioned feeding in LOW

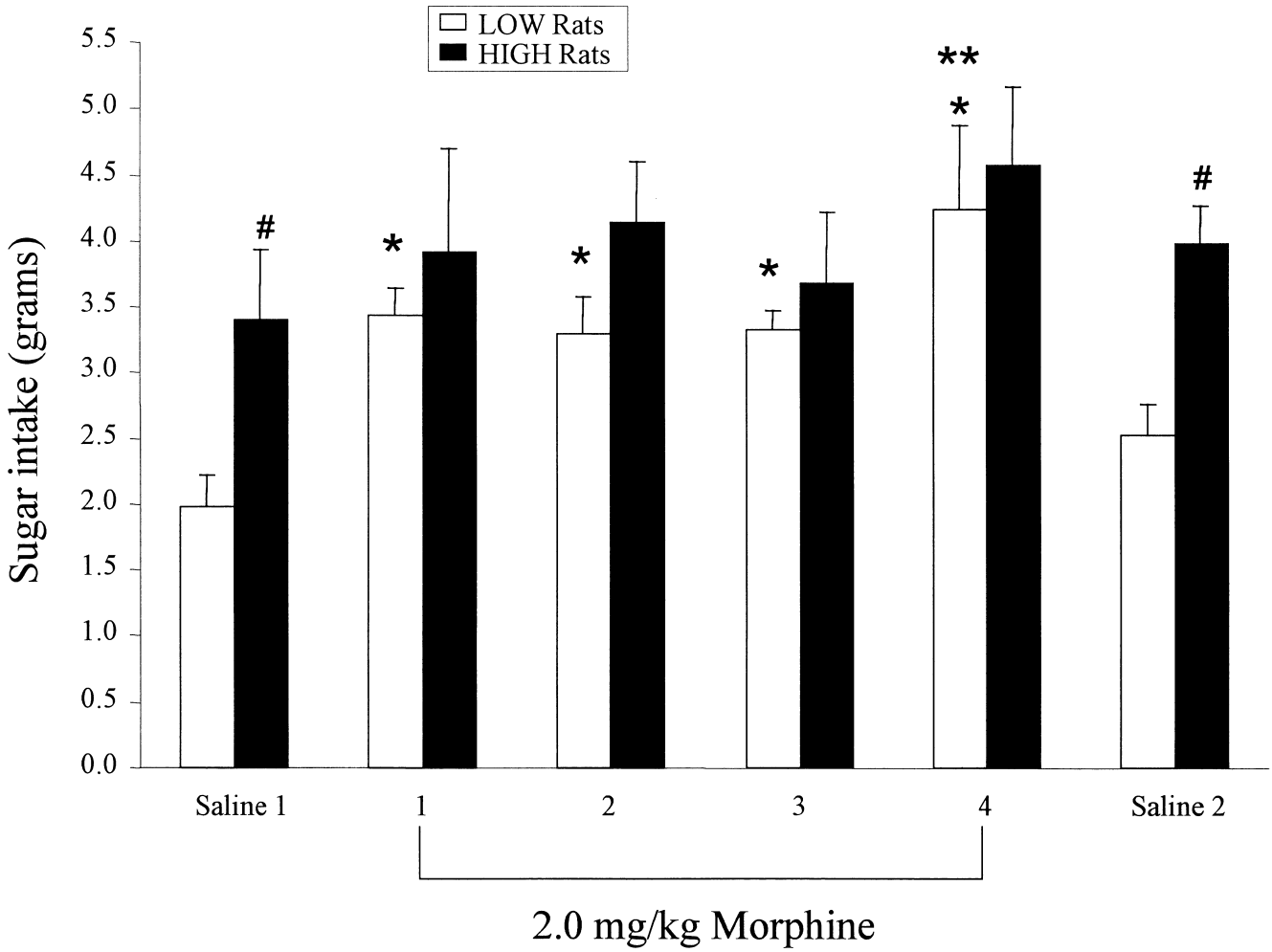

FIG. 4. The average amount of sugar (±SEM) consumed by LOW and HIGH rats following repeated injections of 2.0 mg/kg morphine ($^{\#}p < 0.05$ compared to LOW rats; $^{*}p < 0.05$ compared to saline 1; $^{**}p < 0.05$ compared to saline 2).

rats, as there was no difference in sugar intake between the first and second saline treatments. With regard to HIGH rats, sugar intake did not differ across any of the treatment conditions, $F(5, 40) = 1.22, p > 0.05$ (see Fig. 4).

Locomotor Activity

HIGH rats had higher average daily sugar intake than LOW rats across the 7-day habituation period, $F(1, 12) = 5.791, p < 0.05$. Figure 5 shows that an acute dose of 5.0 mg/kg morphine (day 1) produced higher levels of locomotor in LOW compared to HIGH rats across the last 75 min of the test period, $F(11, 132) = 2.72, p < 0.05$. Overall, LOW rats had higher levels of locomotor activity than HIGH rats, as revealed by a main effect of group, $F(1, 12) = 5.49, p < 0.05$. Further, activity levels were significantly higher in the second half of the test period compared to the first half, as indicated by a main effect of intervals, $F(11, 132) = 9.29, p < 0.05$.

Figure 6 shows the effects of repeated morphine treatments on locomotor activity in LOW and HIGH rats. ANOVA revealed a significant group × day × interval interaction, $F(44, 528) = 1.45, p < 0.05$, a significant day × interval interaction, $F(44, 528) = 5.46, p < 005$, and significant main effects of day, $F(4, 48) = 41.92, p < 0.05$, and interval, $F(11, 132) = 23.18, p < 0.05$. Repeated administrations of morphine produced a triphasic locomotor response pattern that was different from the pattern of activation produced by the acute administration of morphine (day 1). Following acute morphine injection, rats exhibited a period of relative inactivity that was followed by an increase in activity after approximately 90 min. With repeated administrations of morphine, there was a period of significant hyperactivity that immediately followed the injection. This period of hyperactivity was followed by a period of lessened activity that lasted for approximately 60–75 min. Subsequently, there was another increase in locomotor activity that peaked at 90–105 min postinjection. This second peak in activity was equal to the initial burst of activity that was seen immediately following morphine injection.

Figure 7 shows the locomotor response exhibited by LOW and HIGH rats following the acute administration of 2.0 mg/kg morphine. ANOVA revealed a significant group × drug × interval interaction, $F(11, 88) = 2.01, p < 0.05$. Post hoc analyses revealed that, following an initial 15 min period of inhibited activity, morphine stimulated locomotor activity in LOW rats across the test session except at two intervals. In HIGH

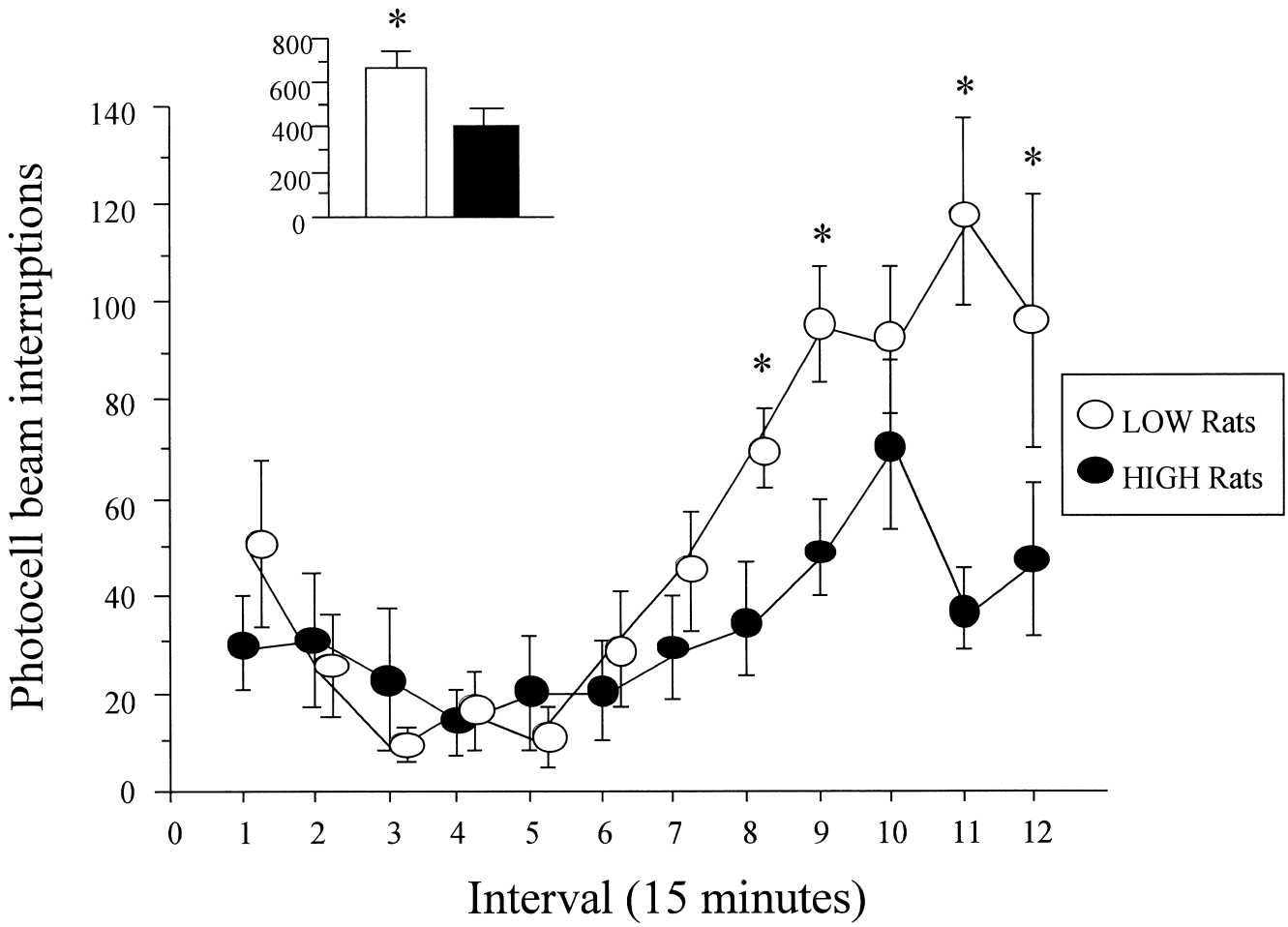

FIG. 5. The average number of photocell beam interruptions (±SEM) exhibited by LOW and HIGH rats following an acute administration of 5.0 mg/kg morphine. Inset: total number of photocell beam interruptions (±SEM) exhibited by LOW and HIGH rats across the 3-h test session following 5.0 mg/kg morphine (*$p < 0.05$ compared to HIGH rats).

rats, morphine produced a significant enhancement in locomotor activity 30 min following the morphine injection, and this increased activity lasted for 105 min. ANOVA also revealed significant main effects of drug, $F(1, 8) = 38.46$, $p < 0.05$, and intervals, $F(11, 88) = 21.63$, $p < 0.05$, and a significant drug × intervals interaction, $F(11, 88) = 4.81$, $p < 0.05$. LOW and HIGH rats did not differ with regard to their overall activity levels following either saline or morphine treatments, as there was no significant main effect of group, $F < 1.0$, nor was there a significant group × drug interaction, $F(1, 8) = 2.62$, $p > 0.05$; there was also no significant group × interval interaction, $F < 1.0$. However, LOW rats tended to exhibit slightly higher levels of locomotor activity than HIGH rats in the first half of the test session. Finally, HIGH rats had higher average daily sugar intake than LOW rats across the seven day habituation period, $t(8) = 5.36$, $p < 0.05$.

DISCUSSION

Food Intake

In the present study, rats that consumed low amounts of sugar under baseline conditions (LOW) exhibited an increase in sugar and chow consumption when treated with morphine. In contrast, rats that consumed high amounts of sugar under baseline conditions (HIGH) were unaffected by morphine treatments. These results demonstrate that LOW and HIGH rats exhibit individual differences in their feeding response to morphine treatments, and that baseline intake level is an important determinant of the feeding response to morphine.

In the present study, morphine stimulated the intake of both chow and sugar in LOW rats. These effects of morphine can be contrasted with those of amphetamine. Previously, it has been shown that low doses of amphetamine (29,31) induced a selective increase in sugar intake in LOW rats given a choice of sugar and lab chow. Thus, morphine produced a generalized stimulatory effect on feeding in LOW rats, in contrast to the sugar selective effect produced by amphetamine. This finding is in agreement with that reported by Evans and Vaccarino (8), and indicates that there must be some divergence in the mechanism(s) regulating the feeding responses to amphetamine and morphine in LOW rats.

The results of the present study show that the largest amount of food is consumed by both LOW and HIGH rats in the 20-min period following injection. Consequently, the majority of feeding is done within the first hour after drug injection, and it is at this time point that morphine produces a sig-

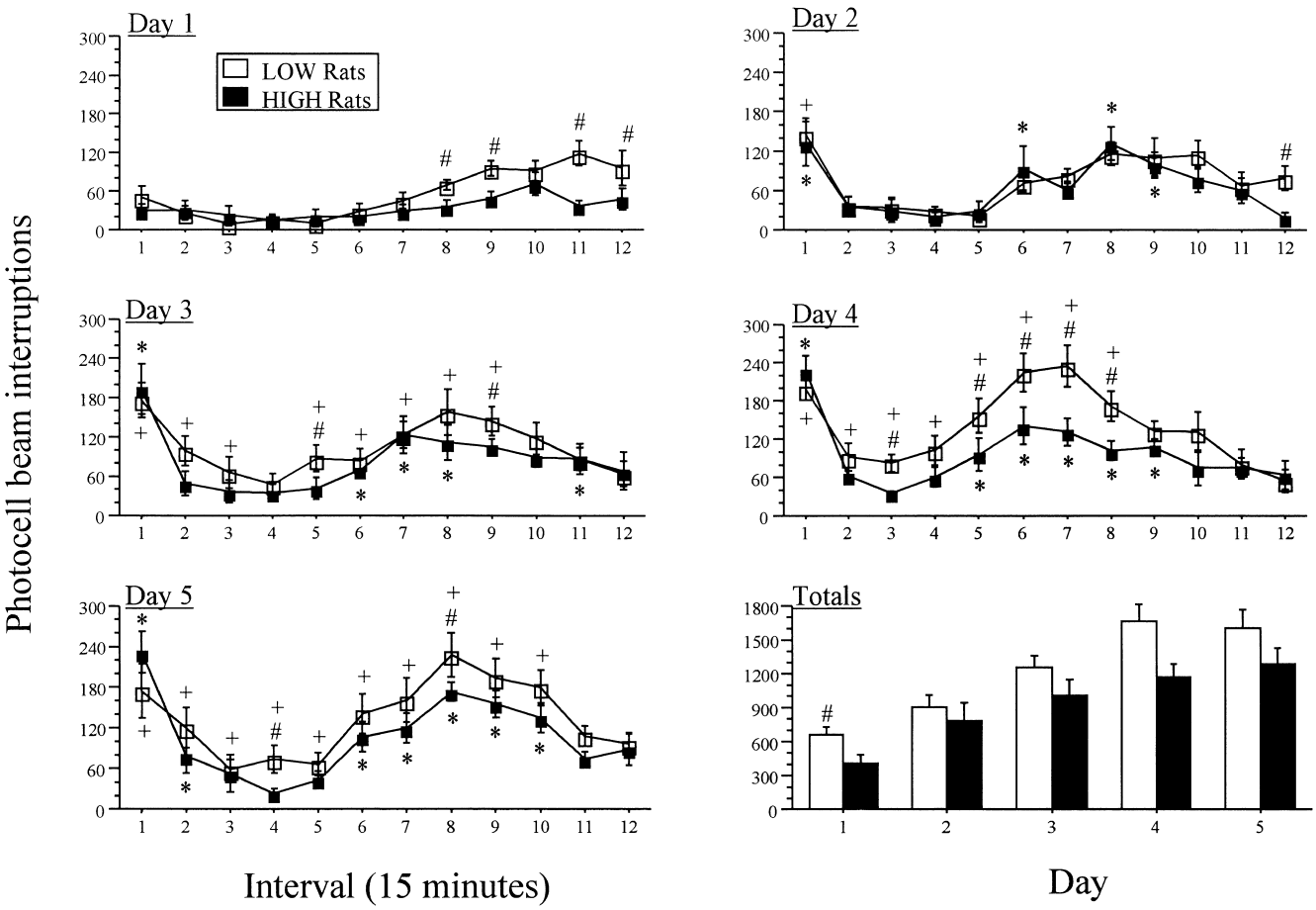

FIG. 6. The average number of photocell beam interruptions (±SEM) exhibited by LOW and HIGH rats following repeated treatment with 5.0 mg/kg morphine ($^{\#}p < 0.05$ compared to HIGH rats; $^{+}p < 0.05$ compared to locomotor activity exhibited by LOW rats on day 1; $^{*}p < 0.05$ compared to locomotor activity exhibited by HIGH rats on day 1).

nificant increase in sugar intake in LOW rats. Furthermore, extending the period of measurement out to 3 h revealed no evidence of a delayed feeding-stimulatory effect produced by morphine in HIGH rats, nor any further significant increases in LOW rats. This temporal profile for the feeding stimulatory effect of morphine is different from that of the locomotor activating effect of morphine in LOW rats, which occurs in the latter half of the 3-h test session. Together, these results suggest that the feeding and locomotor stimulatory effects of morphine may rely on different mechanisms, with different temporal characteristics.

Repeated treatments with 2.0 mg/kg morphine produced a stimulation of sugar intake in LOW, but not HIGH, rats that did not differ across test sessions, indicating a lack of sensitization of the feeding stimulatory effect of morphine in LOW rats. Previously, Morley et al. (22) reported that repeated morphine treatments resulted in a sensitized feeding response. The discrepancy between the present study and that of Morley et al. may be accounted for by the fact that the dose of morphine used by Morley et al. was considerably higher (25 mg/kg) than the dose used in the present study (2.0 mg/kg). As suggested by Morley et al. (22) the sensitized feeding response to repeated treatments with 25 mg/kg morphine probably reflects a tolerance to the sedative effects of morphine that is observed at high doses. A similar explanation may account for the sensitized feeding response to repeated infusions of morphine into the Acb reported by Bakshi and Kelley (3). In the present study, the dose of morphine (2 mg/kg) that was used would be expected to produce minimal sedation. Furthermore, environmental conditioning may be an important factor in the expression of sensitization (3,36) and in the present study, the effects of such conditioning were minimized by the experimental design; all animals received both drug and nondrug treatments in the home cage, which also served as the test environment.

Bakshi and Kelley (3) reported conditioning of feeding following repeated infusions of morphine into the Acb. Thus, rats that received repeated treatments with morphine ate significantly more food in response to saline (or sham injection) challenge after the repeated treatments with morphine compared to a saline challenge prior to the beginning of morphine treatments. In the present study, there was no evidence of a conditioned feeding response in either LOW or HIGH rats following repeated treatments with morphine. A likely explanation for this discrepancy is that, as noted above, the experimental design served to minimize the impact of environmental cues that are critical for the development of conditioning. Another possible explanation for the discrepancy between the present study and that of Bakshi and Kelley is that conditioning may require targeting the Acb directly with morphine. A

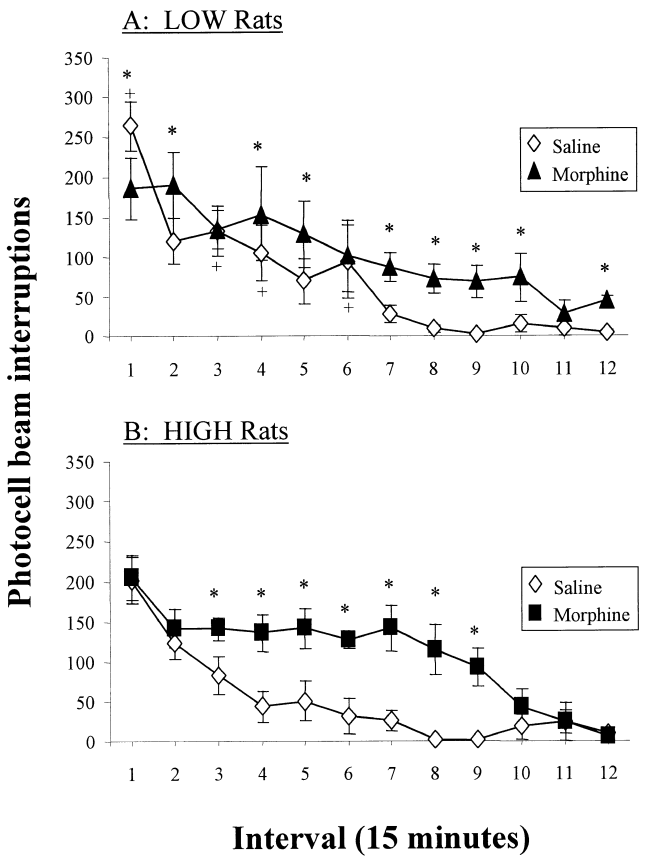

FIG. 7. The average number of photocell beam interruptions (±SEM) exhibited by (A) LOW and (B) HIGH rats following the acute treatment with either saline or 2.0 mg/kg morphine (*$p < 0.05$ compared to saline treatment; $^{+}p < 0.05$ compared to HIGH rats in the saline condition).

third possibility is that conditioning requires a greater stimulation of feeding than was produced in the present study. In this regard, it is of interest to note that morphine-induced feeding was significantly higher in the study by Bahski and Kelley than in the present study.

It is possible that HIGH rats are at a ceiling with regard to their consumption of sugar, and thus further increases in intake are not possible following morphine treatments. Countering this possibility is the finding that intracerebroventricular administration of the potent feeding-stimulatory peptide galanin induced a significant increase in sugar consumption in both LOW and HIGH rats that had levels of intake similar to that observed in the present study (unpublished observation). Also, as noted above, rats are able to consume significantly higher amounts of food than is observed in the present study.

Locomotor Activity

As was the case for food consumption, LOW and HIGH rats exhibited differences in their locomotor response to morphine. When challenged with an acute dose of 5.0 mg/kg, but not 2.0 mg/kg, morphine, LOW rats exhibited significantly higher levels of locomotor activity than HIGH rats. The 5.0 mg/kg dose of morphine produced a biphasic effect on locomotor activity in both LOW and HIGH rats. Following morphine administration there was a period of relative inactivity that lasted for approximately 90 min. This was followed by a gradual increase in activity over the last 90 min of the test session. The difference in locomotor activity exhibited by LOW and HIGH rats was not apparent until the latter half of the test session, when activity levels were at their highest.

The biphasic pattern of activity was not evident at the 2.0 mg/kg dose of morphine. At this dose, morphine stimulated locomotor activity in both groups of rats beginning 15–30 min postinjection, and this activity declined slowly over the test session. HIGH rats had a clearer pattern of activation than LOW rats following treatment with the 2.0 mg/kg dose of morphine, although the levels of locomotor activity were not different between the two groups.

Previous work has shown that moderate to high doses of morphine and other selective μ opioid agonists produce a biphasic effect on locomotor activity (1,20,34) similar to that obtained in the present study. It is important to note that HIGH rats exhibited a prolonged period of inactivity in response to acute morphine when compared to LOW rats. LOW rats exhibited consistently higher levels of locomotor activity during the last 90 min of the test session compared to the first 90 min of the test session. In contrast, HIGH rats exhibited only a brief period of elevated activity 135–150 min post-morphine injection. The fact that HIGH rats showed a prolonged period of inactivity raises the possibility that HIGH rats may be more sensitive than LOW rats to the sedative effects of morphine, thereby exhibiting lowered levels of locomotor activity.

Following repeated administrations of morphine, both LOW and HIGH rats exhibited a sensitized response such that the same dose of morphine produced significantly greater locomotor activity. It is well established that with repeated administrations of morphine and other μ opioid agonists tolerance develops to the depressant effect of morphine while the stimulant effect is enhanced (1,20). In the present experiment, LOW rats exhibited both of these changes following repeated morphine. Repeated morphine treatments in LOW rats resulted in a progressive enhancement of locomotor activity across both the initial sedative phase and the second hyperlocomotive phase following morphine injection. HIGH rats, on the other hand, exhibited only an increase in the stimulant effect of morphine without exhibiting any tolerance to the sedative effect of morphine (see Fig. 6).

Previously, it was shown that HIGH rats exhibited higher levels of locomotor activity in response to amphetamine than LOW rats (32). It has been reported elsewhere that rats that exhibit high levels of activity in response to amphetamine also exhibit high levels of activity in response to 2.0 mg/kg morphine treatment (7). However, the present study found no differences in locomotor activity between LOW and HIGH rats at this dose. Rather, the present study found evidence for an enhanced locomotor response to 5.0 mg/kg morphine in LOW rats that have been shown to be less sensitive to the locomotor activating effect of amphetamine. As discussed above, this dose of morphine appeared to have produced a longer period of sedation in HIGH rats compared to LOW rats. Thus, LOW and HIGH rats may be distinguished by their differential sensitivity to both the locomotor activating and the locomotor depressing effects of morphine.

The expression of individual differences in response to the feeding and motor stimulating effects of morphine reported here might be pertinent to recent findings of individual differences in morphine self-administration (9). Of particular relevance to the present study is the report by Gosnell et al. (10) that rats with a high preference for saccharin self-administered more morphine than rats with low preference for sac-

charin. Extrapolating from this finding, it might be expected that HIGH rats would also self-administer more morphine than LOW rats. However, the results of the present study suggests that LOW rats may be more sensitive to the rewarding effects of morphine than HIGH rats. Therefore, the prediction based on the present results would be that LOW rats would exhibit greater morphine self-administration than HIGH rats. The use of a progressive ratio schedule of morphine self-administration would be useful in determining whether LOW and HIGH rats differ with respect to the reinforcing effects of morphine. A higher breaking point exhibited by one or the other group of rats would indicate an increased sensitivity to the reinforcing effect of morphine.

In summary, results of the present study show that LOW rats exhibit increased sensitivity to the feeding and locomotor stimulating effects of morphine compared to HIGH rats. In contrast, HIGH rats have been shown to be more sensitive than LOW rats to the behavioral activating effect of amphetamine, and to exhibit greater amphetamine-induced Acb-DA release. Taken together, these findings indicate that LOW and HIGH rats may be distinguished by differences in the functioning of both opiatergic and DAergic mechanisms. However, the mechanism(s) through which morphine differentially affects responding in LOW and HIGH rats awaits further elucidation.

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