Long-term effects of food deprivation: II. Impact on morphine reactivity

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Exposure to a series of inescapable shocks elicits a hormonally mediated opioid hypoalgesia in rats. In addition, it has a long-term effect on the opioid system: it increases reactivity to a low dose of morphine. Here we looked at whether another manipulation that elicits a hormonally mediated opioid hypoalgesia—food deprivation—has a similar sensitizing effect. Subjects were placed on a restricted diet for 48 h. Opiate reactivity was then assessed 24 h after food was returned. In Experiment 1, previously food-deprived subjects exhibited a stronger hypoalgesia on the tail-flick test 30 min after an injection of morphine. In Experiment 2, a history of food deprivation increased the duration of morphine hypoalgesia as well as its onset. In Experiment 3, food deprivation per se induced hypoalgesia, but only during the early part of the dark cycle.

It has been shown that exposure to the inescapable shock procedure used to induce behavioral learned helplessness can elicit a strong hypoalgesia in rats (Grau, Hyson, Maier, Madden, & Barchas, 1981; Hyson, Ashcraft, Drugan, Grau, & Maier, 1982; Maier et al., 1980). This hypoalgesia appears to be opioid mediated, because it is blocked by opioid antagonists (i.e., naloxone and naltrexone) and morphine tolerance (Drugan, Grau, Maier, Madden, & Barchas, 1981; Maier et al., 1980). Interestingly, unlike the opioid hypoalgesia observed after a variety of other shock schedules (e.g., Lewis, Cannon, & Liebeskind, 1980; Terman, Shavit, Lewis, Cannon, & Liebeskind, 1984; Watkins, Cobelli, Newsome, & Mayer, 1982; Watkins & Mayer, 1982), that observed after an extended series of inescapable shocks appears to be "hormonally" mediated, because it is attenuated by manipulations that disrupt the functioning of the pituitary-adrenal axis (e.g., adrenalectomy, hypophysectomy, and administration of dexamethasone; see Lewis et al., 1980; Lewis, Tordoff, Sherman, & Liebeskind, 1982; MacLennan et al., 1982).

An extended exposure to inescapable shock also has long-term consequences. Specifically, it sensitizes subjects to becoming hypoalgesic, 24 h later, upon exposure to either mild shock or a low dose of morphine (Grau et al., 1981; Jackson, Maier, & Coon, 1979; Maier et al., 1980). Evidence suggests that the pituitary-adrenal axis plays a critical role in producing this long-term effect. In support of this, it has been shown that the opioid system is not sensitized if subjects are exposed to fewer shocks than are required to activate the hormonal opioid system (Grau et al., 1981; Maier, 1989). Moreover, disrupting the activation of the hormonal opioid system by performing an adrenalectomy or hypophysectomy, or by administer-

ing dexamethasone, prior to inescapable shock exposure blocks the long-term sensitization of the opioid system (MacLennan et al., 1982).

Given that activation of the hormonal opioid system appears to be necessary for one to observe the long-term sensitization effect, one is naturally led to wonder whether or not other manipulations that activate this form of hypoalgesia also sensitize the opioid system. For example, it has been shown that a short period of food deprivation (e.g., 24 h) elicits a strong hypoalgesia (Hamm & Knisely, 1986; Hamm, Knisely, Watson, Lyeth, & Bossut, 1985; McGivern, Berka, Berntson, Walker, & Sandman, 1979; McGivern & Berntson, 1980). This hypoalgesia appears to be mediated by the hormonal opioid system, because it is blocked by naloxone, naltrexone, dexamethasone, adrenalectomy, and hypophysectomy (Hamm & Knisely, 1986; Hamm et al., 1985; McGivern et al., 1979; McGivern & Berntson, 1980). If activation of the hormonal opioid system is sufficient to sensitize the opioid system, subjects that have previously been food deprived should exhibit an exaggerated opioid hypoalgesia in response to either mild shock or a low dose of morphine. Elsewhere, we have demonstrated that previously food-deprived rats do indeed exhibit a much stronger, naltrexone-reversible hypoalgesia following mild shock (Illich, Allen, & Grau, 1991). The present set of experiments was designed to test whether or not food deprivation would also sensitize subjects to the hypoalgesic effect of morphine.

EXPERIMENT 1 Impact of Food Deprivation on Morphine Reactivity

To test whether food deprivation would sensitize the opioid system, half of the subjects were placed on a restricted diet for 48 h. Twenty-four hours after food was returned, we tested pain reactivity with the tailflick test,

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30 min after half of the subjects received a low dose of morphine (1 mg/kg).

Method

Subjects. The subjects were 32 male Sprague-Dawley rats obtained from Harlan (Houston, TX). The rats were 100–120 days old and weighed 420–480 g. They were housed individually and were maintained on a 12:12-h light:dark cycle (lights on at 5:30) with ad-lib food and water, except as was required by the experimental protocol.

Apparatus. During behavioral testing, each rat was restrained in one of two Plexiglas tubes (22 cm long and 6.8 cm in internal diameter). Extending across the base of each tube, 5.3 cm from the top, was a 5.5-cm-wide Plexiglas sheet, which formed a stable platform on which the rat could lie. The front of the tubes were sealed with a clear Plexiglas sheet. To prevent the subject from being distracted by extraneous visual stimuli, the external surface of each tube was covered with duct tape. Thirteen (0.9-cm) holes drilled through the midsection of each tube provided ventilation. A band of adhesive tape was used to seal the rear of each tube. The subject's tail protruded from the rear of the tube, between the band of adhesive tape and the base of the tube.

Pain responsiveness was assessed with the use of a radiant-heat tailflick test. A 375-W movie light (Sylvania, Type EBR) was positioned 18 cm above the base of the apparatus. A condenser lens, which was placed 8 cm below the light, served to focus the light onto the rat's tail. The rat's tail rested within a groove (0.8 cm wide, 0.4 cm deep) cut into an aluminum block. A photocell, positioned below the groove, automatically terminated the trial upon the rat's moving its tail laterally by at least 0.5 cm. The duration of the trial was automatically timed to the nearest 0.01 sec. An 8-sec manual cutoff was used to prevent tissue damage.

Testing was conducted between 7:00 and 11:00 a.m. in an isolated room maintained at 26°C. Ventilation fans provided a background noise level of about 60 dB (SPL).

Procedure. Prior to the experimental treatment, baseline levels of pain reactivity were assessed once a day for 2 days. On each day, subjects were placed in the restraining tubes and allowed 20 min to become acclimated. Four tailflick tests were then given at 2-min intervals. For purposes of statistical analysis, only the last three tailflicks were used. Immediately after testing was completed on Day 2, half of the subjects (deprived) had their food removed. Twenty-four hours later (Day 3), pain reactivity was assessed as described above. After this test, all of the deprived subjects received 9 g of food. Pain reactivity was then tested 24 h later (Day 4), after which the deprived subjects had their food returned. Throughout the food-deprivation period, subjects had ad-lib water. During this period, the nondeprived subjects were treated in the same way, except that they had free access to food. Twenty-four hours after food was returned (Day 5), half of the deprived and nondeprived subjects received an intraperitoneal injection of morphine (1 mg/kg). The remaining subjects were given saline. Ten minutes after the injection, the subjects were placed in the restraining tubes and tested as described above.

Results and Discussion

Prior to the experimental treatments, deprived and nondeprived subjects exhibited similar levels of pain reactivity. The mean tailflick latencies from Day 2 ($\pm SE$) were 5.30 sec (± 0.15) and 5.27 sec (± 0.13) for the nondeprived and the deprived subjects, respectively. An analysis of variance (ANOVA) confirmed that this small difference was not statistically significant [$F(1,30) = 0.03$, $p > .05$].

Tailflick latencies from the 2 days of food deprivation (Days 3 and 4) are depicted in Figure 1. Surprisingly, food deprivation appears to have had little impact on pain reactivity. A repeated measures ANOVA confirmed that the main effect of food deprivation was not statistically significant [$F(1,30) = 0.11$, $p > .05$]. Moreover, neither the main effect of day nor its interaction with deprivation condition approached statistical significance (both F s < 1.28 , $p > .05$).

The levels of pain reactivity observed after morphine or saline in previously food-deprived or nondeprived subjects are illustrated in Figure 2. In the nondeprived controls, morphine had little impact on pain reactivity. In contrast, the low dose of morphine produced hypoalgesia in the previously food-deprived subjects. Importantly, this was true even though the saline-treated deprived and nondeprived subjects exhibited similar levels of pain reactivity. An ANOVA confirmed that food deprivation per se did not have a significant impact on pain reactivity [$F(1,28) = 3.58$, $p > .05$]. The main effect of morphine treatment was also not significant [$F(1,28) = 1.33$, $p > .05$]. There was, however, a significant interaction between morphine treatment and deprivation condition [$F(1,28) = 4.96$, $p < .05$]. Post hoc comparisons with the Newman-Keuls test showed that morphine-treated deprived subjects were hypoalgesic relative to the other three groups ($p < .05$). No other group differences approached statistical significance.

In contrast with others (Hamm et al., 1985; McGivern et al., 1979), we failed to observe any effect of food deprivation per se on pain reactivity. It is not entirely clear why we failed to replicate this effect, since others had obtained it across a wide range of test conditions. One possibility is that the impact of food deprivation is limited to periods during which rats normally consume their food. This would suggest that food deprivation might affect pain reactivity during the dark, but not during the light portion of the light:dark cycle. We evaluated this possibility in Experiment 3.

Even though food deprivation per se had little impact on pain reactivity, it did have a long-term effect on the opioid system. Specifically, it heightened reactivity to morphine.

Figure 1. Baseline tailflick latencies observed in deprived (D, open symbols) and nondeprived (ND, filled symbols) subjects on Days 3 and 4. Error bars depict standard error of the mean.

Figure 2. Levels of pain reactivity observed for nondeprived and deprived subjects after an injection of either 1-mg/kg morphine (filled bars) or saline (open bars). Error bars indicate standard error of the mean.

This supports our hypothesis that food deprivation, like uncontrollable shock, sensitizes the opioid system.

EXPERIMENT 2 Time Course of the Potentiated Morphine Hypoalgesia

From the results of Experiment 1, it is clear that subjects that have previously been food deprived exhibit an exaggerated hypoalgesia 30 min after an injection of morphine. There are two ways in which a prior history of food deprivation could have produced this effect. One possibility is that food deprivation increases the overall impact of morphine, causing the resultant hypoalgesia to develop more rapidly, reach a higher asymptote, and last longer. Alternatively, food deprivation may not alter the overall magnitude or duration of morphine hypoalgesia. Rather, subjects might exhibit an enhanced morphine hypoalgesia 30 min after injection simply because a history of food deprivation increases the onset of morphine hypoalgesia. Such an effect in isolation would not produce any difference in either the maximum hypoalgesic effect of the drug or the duration of the hypoalgesia. In fact, it remains possible that a history of food deprivation not only causes the morphine hypoalgesia to emerge more rapidly, but also causes it to decay more rapidly. To address these alternative explanations, we needed to assess the impact of food deprivation on the duration of morphine hypoalgesia. Thus, in Experiment 2, we looked at the impact of food deprivation on morphine hypoalgesia over a 2.5-h period.

Method

Subjects. The subjects were 36 rats of the same age, sex, and strain as in Experiment 1.

Apparatus. The restraining apparatus and the tailflick device were the same as described for Experiment 1.

Procedure. Half of the subjects in Experiment 2 were placed on a restricted diet for 48 h during which time their food was removed for 24 h; after that, each rat was given a 9-g portion of food, and, 24 h later, ad-lib food was returned. The other half of the subjects had food continuously available during this period. Twenty-four hours after the food was returned, the subjects were placed in the restraining tubes and given two tailflick tests at 15-min intervals. The second test was used to compute the mean baseline levels of pain reactivity. Immediately following baseline testing, subjects were given either an injection of 0.9% saline or a low dose (1 mg/kg) of morphine. Fifteen minutes after the injection, pain reactivity was assessed once every 15 min for 2.5 h with the tailflick test.

Statistical analysis. As one would expect, increasing the interval between each tailflick test from 2 to 15 min increased the variance observed. Three steps were taken to deal with this added variance. First, postinjection scores were collapsed into five 30-min bins. Second, an analysis of covariance (ANCOVA) was used to covary out the variance attributable to differences in baseline levels of pain reactivity. In this analysis, the tailflick scores obtained immediately before the subjects received their injections served as the covariate. Finally, an additional analysis was performed on the change from baseline scores, which were computed by subtracting each subject's baseline score from the tailflick latency recorded immediately prior to injection.

Results and Discussion

An analysis of the baseline scores revealed that the four groups did not differ prior to the injection (all $F_s < 3.02$, $p > .05$). The mean tailflick scores ($\pm SE$) for nondeprived subjects that received saline or morphine were 4.99 (± 0.29) and 5.62 (± 0.45), respectively. The baseline scores for the deprived subjects that received saline or morphine were 6.03 (± 0.37) and 5.42 (± 0.32), respectively.

The impact of morphine over the 2.5-h test period in previously food-deprived and nondeprived subjects is illustrated in Figures 3 and 4. In both figures, it is apparent that morphine induced hypoalgesia in the nondeprived controls. Most importantly, previously food-deprived subjects exhibited an even greater hypoalgesia, and this was true at the start (15–30 min after injection), middle (75–90 min), and end (135–150 min) of testing. These impressions were confirmed by both an ANCOVA on the raw data and an ANOVA performed on the change from baseline scores. In both cases the main effect of drug treatment (both $F_s > 20.74$, $p < .001$) and its interaction with deprivation condition (both $F_s > 6.50$, $p < .05$) were significant. The main effect of deprivation treatment was not significant (both $F_s < 0.32$, $p > .05$). In both cases, post hoc comparisons of the group means with the Newman-Keuls test showed that the two morphine-treated groups were hypoalgesic relative to the saline treated controls and that a significantly greater morphine hypoalgesia was observed in the previously food-deprived subjects ($p < .05$). None of the other group differences approached statistical significance.

Not surprisingly, the within-subject terms of both the ANCOVA and the ANOVA showed that the impact of drug treatment depended on time of testing (both $F_s > 5.93$, $p < .001$). The ANOVA performed on the change

Figure 3. Mean tailflick latencies observed every 30 min for a period of 2.5 h in deprived (D, open symbols) and nondeprived (ND, filled symbols) subjects that were treated with either morphine (M, squares) or saline (S, circles). Error bars indicate standard error of the mean.

from baseline scores also revealed a significant main effect of time of testing [$F(4,128) = 4.22, p < .005$]. None of the other within-subject terms approached statistical significance (all $F_s < 1.42, p > .05$).

Thus, subjects that had previously been food deprived exhibited an exaggerated morphine hypoalgesia, and this was true at the start (15–30 min after injection), middle (75–90 min), and end (135–150 min) of testing. This finding suggests that the results from Experiment 1 do not simply reflect an increase in the rate at which previously food-deprived rats become hypoalgesic. Rather, food deprivation appears to increase the effectiveness of the opiate so that it produces a hypoalgesia that not only comes on more rapidly but has a higher asymptote and lasts longer.

In contrast with the results of Experiment 1, nondeprived subjects appeared hypoalgesic 30 min after they received morphine. A number of procedural differences may account for this discrepancy. Perhaps the most obvious is that the subjects in Experiment 2 were not preexposed to the test apparatus. This could have increased the levels of stress during testing, which in turn may have potentiated the hypoalgesia observed in the nondeprived controls.

EXPERIMENT 3 Impact of Food Deprivation on Pain Reactivity

The hypothesis that motivated these experiments was that manipulations that elicit a hormonally mediated opioid hypoalgesia sensitize the opioid system. The work reported here, and previously (Illich et al., 1991), suggests that food deprivation does indeed sensitize the opioid system. However, we have routinely failed to replicate the basic finding that motivated these experiments: that food dep-

rivation induces hypoalgesia (Hamm & Knisely, 1986; McGivern et al., 1979). Elsewhere, we (Illich et al., 1991; Illich & Grau, 1990, 1991) and others (e.g., Fredrickson, Burgis, & Edwards, 1977) have noted that the magnitude of conditioned hypoalgesia, mild shock-induced hypoalgesia, and morphine hypoalgesia varies considerably, depending on the time of day at which subjects are tested; in all cases, a stronger hypoalgesia is observed when subjects are tested in the early portion of the dark phase than when they are tested in the early portion of the light phase. Given these observations, we wondered whether we might routinely have failed to observe a significant effect of food deprivation per se on pain reactivity simply because we tested subjects during the early portion of the light phase. In Experiment 3, we evaluated this possibility by assessing the impact of food deprivation on pain reactivity three times each day, at 7:00 a.m., 3:00 p.m., and 11:00 p.m.

A detailed inspection of previous studies in which food-deprivation-induced hypoalgesia had been observed suggested another reason why we might have failed to observe this effect. In these studies, unlike our own, the subjects were housed in suspended cages with metal grid floors. In contrast, our subjects were housed in tubs that contained standard laboratory litter made from wood shav-

Figure 4. Change from baseline scores observed every 30 min for a period of 2.5 h in nondeprived (upper panel) and deprived (lower panel) subjects that were treated with either morphine (M, filled symbols) or saline (S, open symbols).

ings. We thought that such a difference might be important, because rats are coprophagic and our food-deprived subjects frequently chewed on their bedding material. To assess whether this variable would influence the magnitude of the food-deprivation effect, half of the subjects in Experiment 3 were housed in tubs with metal grid floors, and the other half were housed in tubs containing litter.

Method

Subjects. The subjects were 24 rats of the same age, sex, and strain as in the previous experiments.

Apparatus. The apparatus was the same as in the previous experiments.

Procedure. Prior to the start of Experiment 3, half the subjects were housed on laboratory litter, and the other half were housed on metal grid floors. Baseline levels of pain reactivity were assessed four times over the course of a single 24-h period (Day 1) at 7:00 a.m., 3:00 p.m., 11:00 p.m., and 7:00 a.m. again. During each test period, the subjects were placed in the restraining tubes and given four tailflicks at 2-min intervals. As before, the first tailflick latency was discarded. Immediately after the last session of baseline testing, half of the rats in each housing condition were food deprived. Pain reactivity was then assessed at 3:00 p.m., 11:00 p.m., and 7:00 a.m. (Day 2). Immediately after the 7:00 a.m. test, these subjects were given 9 g of food. Over the next 24-h period (Day 3), the subjects were tested in the same manner as on the previous day. They then had their food returned and were tested three more times over a 24-h period (Day 4). The other subjects were treated in the same way, except that they had food continuously available.

Results and Discussion

We found that housing condition (litter vs. grid floors) did not affect pain reactivity or the magnitude of the food-deprivation effect (all F s < 2.04, p > .05). Consequently, we collapsed the data across housing conditions.

Before food deprivation, no difference existed between the groups in either baseline tailflick scores or weight. At 7:00 a.m., immediately before the food-deprived subjects had their food removed, the mean baseline tailflick scores ($\pm$ SE) were 6.11 ($\pm$.36) and 5.92 ($\pm$.27) for the nondeprived and deprived groups, respectively. The mean weights ($\pm$ SE) for the nondeprived and deprived groups were 431 ($\pm$ 5.71) and 428 ($\pm$ 4.59), respectively. Neither the difference in tailflick latencies nor the difference in weight approached statistical significance (both F s < .23, p > .05).

The tailflick scores observed over the next 3 days (Days 2–4) are depicted in Figure 5. It appears that food deprivation had little impact on pain reactivity until the 3rd day of testing (24–48 h after food was removed), and here the effect was limited to the 11:00 p.m. test point. This difference vanished on Day 4 after food was returned. An ANOVA confirmed that the impact of food deprivation depended on the time of day at which subjects were tested [$F(2,44) = 3.63$, p < .05]. The main effects of time of day, deprivation treatment, and day of testing were not statistically significant (all F s < 2.02, p > .05). In addition, the main effect of day did not interact significantly with deprivation treatment, time of day, or the combination of the two (all F s < 1.84, p > .05). To determine when food deprivation affected pain reactivity, a Bonferroni

Figure 5. Levels of pain reactivity observed in deprived (D, open symbols) and nondeprived (ND, filled symbols) subjects as a function of time of day over the 2 days on which diet was controlled (Days 2 and 3) and for the following 24-h period during which all subjects were maintained on ad-lib food (Day 4). Error bars indicate standard error of the mean.

t test was used to compare the deprived and nondeprived subjects at each time point. This statistic was employed because it maintains the error rate at the .05 level (two-tailed test) for a family of contrasts. This test revealed that the deprived subjects were hypoalgesic relative to the nondeprived subjects at 11:00 p.m. on Day 3 ($t = 3.06$, p < .05). No other comparisons were significant (all t s < 2.41, p > .05).

The impact of food deprivation on weight is depicted in Figure 6. It is clear that food deprivation induced a rapid weight loss and that after food was returned the difference between the deprived and nondeprived rapidly vanished. An ANOVA showed that the main effects of deprivation condition, day, and time of day were all statistically significant (all F s > 5.43, p < .05). In addition, all the higher order interactions were significant (all F s > 7.67, p < .001).

Figure 6. The diurnal fluctuations in weight observed in food-deprived (D, open symbols) and nondeprived (ND, filled symbols) subjects for the 2 days on which diet was restricted (Days 2 and 3) and for the 24-h period after food was returned to the previously food-deprived subjects (Day 4). Error bars indicate standard error of the mean.

Close inspection of Figure 6 reveals an unexpected outcome: nondeprived subjects lost a small amount of weight during the course of the experiment. Although the amount lost was small ($M = 18$ g, a 4.1% reduction in average body weight), the weight reduction was observed in 12 out of the 12 subjects [$F(1,11) = 107.8, p < .001$]. An obvious explanation as to why this was observed is that the stress associated with repeated testing caused a slight reduction in food intake. To the extent that our test procedure does induce some stress, this effect could make it more difficult to resolve the impact of other mild stressors.

As in our previous studies, food deprivation had little impact on pain reactivity when testing was conducted in the early portion of the light cycle. It did, however, induce hypoalgesia when the subjects were tested during the early portion of the dark cycle.

GENERAL DISCUSSION

The present set of experiments were designed to evaluate whether food deprivation, like inescapable shock, sensitizes the opioid system. We tested this hypothesis by assessing the impact of food deprivation on morphine hypoalgesia. Experiment 1 showed that previously food-deprived subjects exhibit a heightened response to morphine. Experiment 2 showed that this effect does not simply reflect an increase in the rate at which previously food-deprived subjects become hypoalgesic—a history of food deprivation also increases the asymptote and duration of morphine analgesia.

Although others (Hamm et al., 1985; McGivern et al., 1979) have found that food deprivation per se elicits a strong hypoalgesia, we failed to replicate this basic effect in Experiment 1. Because hypoalgesic effects are often much smaller when subjects are tested during the early portion of the light cycle than when they are tested during the early portion of the dark cycle, we speculated that we might have failed to observe a food-deprivation effect simply because subjects were tested during the early portion of the light cycle. In support of this, in Experiment 3 we found that on the 2nd day of food deprivation, subjects were hypoalgesic during the early portion of the dark cycle. Thus, we were able to replicate the finding that food deprivation induces hypoalgesia. However, in contrast with previous reports (McGivern et al., 1979), this effect was only observed during the early portion of the dark cycle. It is not entirely clear why others have been able to obtain food-deprivation-induced hypoalgesia during the early portion of the light cycle and why we observed little difference at this time point. Factors that might account for this discrepancy include: the way in which subjects are restrained during testing; when animal care is performed; the strain of rat used; and the age of the rat at the onset of the experiment.

In the present article, we have shown that a manipulation with which others (Hamm & Knisely, 1986; Hamm et al., 1985; McGivern et al., 1979) have elicited a hor-

monally mediated opioid hypoalgesia—food deprivation—sensitizes subjects to the hypoalgesic effect of morphine. Elsewhere (Illich et al., 1991), we have demonstrated that the same manipulation augments the opioid hypoalgesia observed after mild shock. These findings suggest that our previous work based on the intermittent shock paradigm may have considerable generality. Supporting this, others (Appelbaum & Holtzman, 1984) have shown that another manipulation that elicits this form of hypoalgesia, immobilization stress (Amir & Amit, 1978, 1979), sensitizes rats to the hypoalgesic effects of morphine. Moreover, like our food-deprivation effect, immobilization stress has a long-term impact on the opioid system; it sensitizes the system for up to 168 h (Calcagnetti & Holtzman, 1990).

There are a variety of ways in which these manipulations could alter opioid reactivity. One simple hypothesis is that the stress of food deprivation or immobilization increases receptor affinity. However, at least for immobilization stress, evidence suggests that this type of modification is not involved (Appelbaum & Holtzman, 1985). Alternatively, a history of stress may elicit the release of an opioid that in itself has little hypoalgesic effect (e.g., adrenal enkephalins), but that is capable of potentiating the hypoalgesic effect of other opioid agonists by means of a multiplicative interaction (Grau, 1987; Yeung & Rudy, 1980). Others have suggested that corticosterone may play a role in sensitizing the opioid system, possibly by enhancing serotonergic transmission (MacLennan et al., 1982). This hypothesis fits well with the finding that valine, a drug that blocks the uptake of the precursor to serotonin (tryptophan), prevents immobilization stress from sensitizing the opioid system (Kelly & Franklin, 1985). Clearly, further work is needed to elucidate the physiological and neurochemical modifications that underlie opioid sensitization.

We have framed the present study in terms of our past work on learned helplessness and the activation of the hormonal form of opioid hypoalgesia. However, the findings are also relevant to the more general issue of how food deprivation can influence addictive behavior. For example, evidence suggests that food-deprived subjects find a variety of drugs more reinforcing than do nondeprived controls (Asghar, 1986). In the present study, we have extended this work by showing that a very mild food-deprivation schedule can influence morphine reactivity. More importantly, we have demonstrated that food deprivation can have long-term consequences; it can influence opioid reactivity after food has been returned. This finding may have important clinical implications, for it suggests that people who have a history of food deprivation may be hyperreactive to an opiate. Such an effect could alter the reinforcing properties of the drug, and, consequently, addictive behavior. Further work is needed to determine whether or not a prior history of food deprivation alters the motivational or reinforcing consequences of an opiate. We are currently pursuing these issues.

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