Altered Vulnerability to Acute Opiate Withdrawal Following Stress: Roles of N-Methyl-D-Aspartate and Glucocorticoid Receptors

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Five experiments studied the modulation of acute opiate withdrawal by restraint stress. Rats were subjected to a 2-hr restraint stress, and 1, 3, or 7 days later they received a single injection of morphine followed by injection of naloxone. Naloxone precipitated a withdrawal syndrome. This syndrome was enhanced when it occurred 1 day after stress but was reduced when it occurred 7 days after stress. The enhancement of withdrawal by restraint stress was prevented by treatment with the N-methyl-D-aspartate (NMDA) receptor antagonist MK801 or the glucocorticoid receptor antagonist RU486 prior to stress. Together these experiments show that restraint stress alters vulnerability to opiate withdrawal and identify activation of NMDA and glucocorticoid receptors as causal to this vulnerability.

*Keywords:* stress, withdrawal, sensitization, MK801, RU486

Stress has a profound influence on opiate and psychostimulant dependence. Animal models have consistently shown that exposure to stressors such as intermittent footshock (Goeders & Guerin, 1994; Shaham & Stewart, 1994), restraint (Deroche et al., 1992), food restriction (Deroche et al., 1993), social isolation (Deroche, Piazza, LeMoal, & Simon, 1994), and social defeat (Covington & Miczek, 2001; Haney, Maccari, LeMoal, Simon, & Piazza, 1995) facilitate the behavioral impact as well as the intravenous self-administration of opiates and psychostimulants. Moreover, such stressors can induce relapse to drug seeking in animals previously trained to self-administer opiates or psychostimulants (Ahmed & Koob, 1997; Erb, Shaham, & Stewart, 1996; Mantch & Goeders, 1999; Shaham & Stewart, 1995). Although these interactions have typically been observed with prolonged or multiple exposures, there is evidence that similar interactions can also occur following acute exposure to stress and drugs of abuse. For example, Will, Watkins, and Maier (1998) exposed rats to a single session of 100 inescapable tailshocks and commenced conditioned place preference training based on injection of morphine at varying intervals following these shocks. Their results showed that the single session of inescapable shock facilitated acquisition of a morphine-induced place preference when that acquisition occurred up to 7 days after shock.

These interactions occur, at least in part, because of shared neural mechanisms between stress and drugs of abuse (e.g., Lu, Shepard, Hall, & Shaham, 2003; Marinelli & Piazza, 2002; Piazza & LeMoal, 1998). Opioid peptides (e.g., Zurita, Martijena, Cuadra, Brandao, & Molina, 2000), noradrenaline (e.g., Shaham, Highfield, Delfs, Leung, & Stewart, 1997), corticotropin-releasing hormone (e.g., Erb & Stewart, 1999), and glucocorticoids (e.g., Piazza & LeMoal, 1997) are all critical for the interactions between stress and drugs of abuse. For example, surgical and pharmacological suppression of glucocorticoids prevents the enhancement of morphine-conditioned place preference by uncontrollable stress (Der-Avakian et al., 2005). Moreover, there is evidence that these interactions occur because of common effects on neurotransmission in the mesolimbic dopamine pathway. For example, Saal, Dong, Bonci, and Malenka (2003) reported that exposure to either drugs of abuse (e.g., morphine, cocaine, or amphetamine) or forced swim stress increased the strength of excitatory amino-acid synapses at rat midbrain dopamine neurons. This potentiation of excitatory amino-acid synapses by stress could be prevented by pretreatment with either the noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist MK801 or the glucocorticoid receptor antagonist RU486 (Saal et al., 2003). These results were interpreted to mean that stress and drugs of abuse produce similar alterations in dopamine neurotransmission so that prior exposure to stress may prime, sensitize, or otherwise increase this neurotransmission in response to drugs of abuse.

In contrast to the well-documented interactions between stress and opiate reward, considerably less attention has been directed toward possible interactions between stress and opiate withdrawal. Drug withdrawal can play an important role in maintaining persistent drug taking (e.g., Hutcheson, Everitt, Robbins, & Dickinson, 2001). It follows that manipulations that alter the severity of drug withdrawal will have an important impact on drug self-administration and persistent drug taking. Consistent with interactions between stress and opiate withdrawal, Shaham (1993) reported that rats repeatedly exposed to restraint stress prior to drug self-administration showed augmented drug self-administration and augmented withdrawal. Likewise, Williams, Drugan, and Maier (1984) reported that rats that received two daily sessions of 8 inescapable shocks showed enhanced withdrawal behaviors 24 hr later when injected with morphine followed by a naloxone challenge. Indeed, prolonged exposure to stress, and consequent prolonged activation of endogenous opioid systems, may itself
produce expression of withdrawal-like behaviors. For example, Miczek, Thompson, and Shuster (1986) subjected mice to 7 days of stress by using the resident–intruder preparation. These mice displayed opiate withdrawal-like behaviors when administered an opioid receptor antagonist in the absence of any opiate agonist. Together these and other (Manik & Katz, 1984) findings clearly support the possibility that stress may prime, sensitize, or otherwise increase vulnerability to opiate withdrawal. The aim of the present series of experiments was to characterize this relationship between stress and opiate withdrawal.

Opiate-naive rats were first subjected to 2-h restraint stress. Twenty-four hours later they were injected with morphine followed 30 min later by naloxone. We selected an acute opiate withdrawal preparation to study stress–withdrawal interactions because prior research has shown that a history of opiate exposures alters responsivity to restraint stress (Blatchford, Diamond, Westbrook, & McNally, in press). In this way, it was possible to ensure that any differences between groups in withdrawal severity were not due to the effects of the opiate history on stress responsivity (i.e., increasing vulnerability to the stress). In Experiment 1, we studied the effects of a 2-hr exposure to restraint stress on opiate withdrawal precipitated 24 hr after stress. In Experiment 2, we studied the time course of the modulation of opiate withdrawal by stress. The role of NMDA receptors in the modulation of opiate withdrawal by stress was studied in Experiment 3. In Experiment 4, we studied the role of glucocorticoid receptors in the modulation of opiate withdrawal by stress. Finally, in Experiment 5, we studied the effects of NMDA and glucocorticoid receptor antagonism on opiate withdrawal in the absence of restraint stress to ensure that the effects of these drugs were specific to the interaction between stress and opiate withdrawal.

Method

Subjects

Adult male Wistar rats (280–350 g) were obtained from a commercial supplier (Gore Hill Research Laboratories, Sydney, New South Wales, Australia). After arrival, rats were housed in groups of 6–8 in plastic cages maintained on a 12:12-hr light–dark cycle (lights on at 7:00 a.m.) and were allowed access to water and food ad libitum. The rats were handled (1–2 min per rat per day) for 3 days to habituate them to the experimenter. The procedures used in these experiments were approved by the Animal Care and Ethics Committee at the University of New South Wales.

Apparatus and Drugs

Four buckets (29 cm diameter × 50 cm height) were used as test chambers. Four Plexiglas cylinders (6 cm diameter; 21 cm length) were used as restrainers. Morphine HCl (a generous gift from Glaxo-Smith-Kline, Melbourne, Victoria, Australia) was dissolved in sterile 0.9% (wt/vol) saline to obtain a concentration of 15 mg/ml and was injected subcutaneously in a volume of 1 ml/kg. Naloxone HCl (Sigma, Sydney, New South Wales, Australia) was dissolved in sterile 0.9% (wt/vol) saline to obtain a concentration of 5 mg/ml and was injected subcutaneously in a volume of 1 ml/kg. Morphine HCl (a generous gift from Glaxo-Smith-Kline, Melbourne, Victoria, Australia) was dissolved in sterile 0.9% (wt/vol) saline to obtain a concentration of 15 mg/ml and was injected subcutaneously in a volume of 1 ml/kg.

Procedure

Experiment 1: Interactions between stress and opiate withdrawal. Thirty-two rats were randomly allocated to one of four groups: no stress–saline, stress–saline, no stress–morphine, and stress–morphine (n = 8 per group). In the morning and afternoon of Day 1, rats were transported to the laboratory and placed in the test chambers for 30 min. This was done to familiarize the animals with the test chambers. On Day 2, all rats were transported to a different laboratory. Rats in the stress groups were placed in restrainers for 2 hr, whereas rats in the no-stress groups were briefly handled and returned to their home cages. On Day 3, rats were transported to the test laboratory. Upon arrival, all rats were briefly removed from their home cage, injected, and then returned to their home cage. Rats in the morphine groups were injected with 15 mg/kg morphine, whereas rats in the saline groups were injected with saline. Thirty minutes later, all rats were removed from their home cages, injected with 5 mg/kg naloxone, and then placed in the test chambers. Rats were observed continuously for signs of opiate withdrawal for 15 min. An observer scored behavior for the following signs of opiate withdrawal: wet dog shakes, head shakes, teeth chattering, diarrhea, salivation, secretions from the eyes or nose, ptosis, ejaculation or genital grooming, postural abnormalities (lying on the belly), and irritability on handling (Blasig, Herz, Reinhold, & Ziegglansberger, 1973). All signs were counted. Salivation, secretions from the eyes or nose, ptosis, and postural abnormalities, if observed, counted once only within each 5-min period as a result of difficulties in distinguishing individual bouts. The total number of withdrawal signs observed was calculated.

Experiment 2: Time course of interactions between stress and opiate withdrawal. Thirty-two rats were randomly allocated to one of four groups: control, 1 day, 3 days, and 7 days (n = 8 per group). Twice on Day 1, rats were transported to the laboratory and placed in the test chambers for 30 min as described above. On Day 2, rats in the 1-day, 3-days, and 7-days groups were placed in restrainers for 2 hr. Rats in the control group were briefly handled before being returned to their home cage. Rats were transported to the test laboratory either 1 day, 3 days, or 7 days later according to their group allocations. Rats in the control group were transported to the test laboratory 1 day (n = 2), 3 days (n = 3), or 7 days (n = 3) later. Upon arrival, rats were briefly removed from their home cage, injected with 15 mg/kg morphine, and then returned to their home cage. Thirty minutes later, they were removed from their home cages, injected with 5 mg/kg naloxone, and then placed in the test chambers. Rats were observed continuously for signs of opiate withdrawal for 15 min as described above.

Experiment 3: Role of NMDA receptors in interactions between stress and opiate withdrawal. Forty rats were randomly allocated to one of five groups: control, 1 day–saline, 1 day–MK801, 7 days–saline, and 7 days–MK801 (n = 8 per group). Twice on Day 1, rats were transported to the laboratory and placed in the test chambers for 30 min as described above. On Day 2, rats in the 1 day–saline and 7 days–saline groups were injected intraperitoneally with saline, whereas rats in the 1 day–MK801 and 7 days–MK801 groups were injected intraperitoneally with 0.1 mg/kg MK801. Thirty minutes later, rats in these groups were placed in restrainers for 2 hr. Rats in the control group were briefly handled before being returned to their home cages. Rats were transported to the laboratory and tested either 1 day or 7 days later according to their group allocations. Half of the rats in the control group were tested at 1 day, and the remainder were tested at 7 days. Upon arrival, rats in all groups were briefly removed from their home cage, injected with 15 mg/kg morphine, and then returned to their home cage. Thirty minutes later, rats were removed from their home cages, injected with 5 mg/kg naloxone, and then placed in the test chambers. Rats were observed continuously for signs of opiate withdrawal for 15 min as described above.

Experiment 4: Role of glucocorticoid receptors in the interaction between stress and opiate withdrawal. Thirty-five rats were randomly allocated to one of five groups: control, 1 day–vehicle, 1 day–RU486, 7 days–vehicle, and 7 days–RU486 (n = 7 per group). Twice on Day 1, rats
were transported to the laboratory and placed in the test chambers for 30 min as described above. On Day 2, rats in the 1-day–vehicle and 7 days–vehicle groups were injected subcutaneously with DMSO vehicle, whereas rats in the 1-day–RU486 and 7 days–RU486 groups were injected subcutaneously with 40 mg/kg RU486. This dose was chosen because it has previously been shown to prevent the effects of swim stress at excitatory amino-acid synapses in the midbrain (Saal et al., 2003). Thirty minutes later, rats in these groups were placed in restrainers for 2 hr. Rats in the control group were briefly handled before being returned to their home cage. Rats were transported to the test laboratory either 1 day or 7 days later according to their group allocations. Rats in the control group were transported to the laboratory and tested either 1 day (n = 4) or 7 days (n = 3) later. Upon arrival, rats in all groups were briefly removed from their home cage, injected with 15 mg/kg morphine, and then returned to their home cage. Thirty minutes later, rats were removed from their home cages, injected with 5 mg/kg naloxone, and then placed in the test chambers. Rats were observed continuously for signs of opiate withdrawal for 15 min as described above.

Experiment 5: The effects of MK801 and RU486 on opiate withdrawal. Thirty-two rats were randomly allocated to one of four groups: saline, MK801, DMSO, and RU486. Twice on Day 1, rats were transported to the laboratory and placed in the test chambers for 30 min as described above. On Day 2, the rats were injected subcutaneously with DMSO or 40 mg/kg RU486 or intraperitoneally with saline or 0.1 mg/kg MK801. The following day, rats were tested. They were transported to the laboratory, and upon arrival, they were briefly removed from their home cage, injected with 15 mg/kg morphine, and then returned to their home cage. Thirty minutes later, rats were removed from their home cage, injected with 5 mg/kg naloxone, and then placed in the test chambers. Rats were observed continuously for signs of opiate withdrawal for 15 min as described above.

Statistical Analysis

The data were analyzed by means of planned orthogonal contrasts controlling the decision-wise error rate (α) at 0.05 with the methods described by Harris (1994).

Results

Experiment 1: Interactions Between Stress and Opiate Withdrawal

The mean (+ SEM) number of withdrawal signs observed on test is shown in Figure 1. From inspection, it is clear that challenge injection of naloxone among animals injected with morphine precipitated an acute withdrawal syndrome (the no stress–morphine group) as compared with animals not injected with morphine (the no stress–saline group). This acute precipitated withdrawal syndrome differed from that previously described in animals chronically exposed to morphine (e.g., McNally & Akil, 2002b). The acute withdrawal syndrome was characterized predominantly by teeth chattering, whole body or head shakes, genital grooming, and postural abnormalities (e.g., lying on the belly). In contrast to the withdrawal syndrome precipitated from chronic morphine, there were no instances of escape jumping, salivation, or secretions from the eyes and nose, and there were only a few instances of ptosis or diarrhea.

There was a significant main effect for morphine versus saline, F(1, 28) = 94.5, p < .05. Thus, injection of naloxone precipitated signs of opiate withdrawal that were significantly greater among rats previously injected with morphine than rats previously injected with saline. There was a significant main effect for stress versus no stress, F(1, 28) = 9.3, p < .05. Thus, injection of naloxone precipitated signs of opiate withdrawal that were significantly greater among rats previously subjected to restraint stress. Finally, there was a significant interaction between stress versus no stress and morphine versus saline, F(1, 28) = 7.9, p < .05. In other words, the effect of restraint stress was to selectively enhance the withdrawal syndrome among the stress–morphine group. This was confirmed by a subsequent analysis that showed a significant difference between the stress–morphine and no stress–morphine groups, F(1, 28) = 17.3, p < .05. This enhancement was especially pronounced for teeth chattering, postural abnormalities, genital grooming, and ptosis and was less pronounced for body or head shakes.

Experiment 2: Time Course of Interactions Between Stress and Opiate Withdrawal

The mean (+ SEM) number of withdrawal signs observed on test is shown in Figure 2. From inspection, it is apparent that restraint stress enhanced withdrawal from morphine precipitated 1 day but not 3 or 7 days later. Indeed, the opiate withdrawal syndrome appeared to be reduced when it occurred 7 days after restraint stress. These observations were confirmed by the statistical analysis. There was a significant increase in withdrawal among rats in the 1-day group compared with rats in the control group, F(1, 28) = 22.4, p < .05. This enhancement was especially pronounced for teeth chattering, genital grooming, and ptosis and was less pronounced for postural abnormalities for body or head shakes. There was no significant difference in withdrawal among rats in the 3-days group as compared with rats in the control group, F(1, 28) < 1, p < .05. Finally, there was a significant decrease in withdrawal among rats in the 7-days group as compared with rats in the control group, F(1, 28) = 7.7, p < .05. This reduction was especially pronounced for teeth chattering, genital grooming, and postural abnormalities.

Experiment 3: Role of NMDA Receptors in the Interaction Between Stress and Opiate Withdrawal

The mean (+ SEM) number of withdrawal signs observed on test is shown in Figure 3. From inspection, it can be seen that...
withdrawal from morphine was enhanced when it was precipitated 1 day after restraint but was reduced when it occurred 7 days after restraint. Injection of the noncompetitive NMDA receptor antagonist MK801 prior to restraint stress appeared to abolish the enhancement of opiate withdrawal but left unaffected the reduction in opiate withdrawal. The statistical analysis confirmed these observations. There was a significant increase in the number of withdrawal signs observed among the 1 day–saline group as compared with the control group, \( F(1, 34) = 7.2, p < .05 \), but a significant decrease in the number of withdrawal signs observed among the 7 days–saline group as compared with the control group, \( F(1, 34) = 7.9, p < .05 \). There was also a significant decrease in the number of withdrawal signs observed among the 1 day–RU486 group as compared with the control group, \( F(1, 30) = 7.7, p < .05 \). Thus, glucocorticoid receptor antagonism during restraint stress prevented the enhancement of withdrawal 1 day later.

There was, however, no significant difference in the number of withdrawal signs observed among the 7 days–MK801 group as compared with the 7 days–saline group, \( F(1, 34) < 1, p < .05 \). Thus, NMDA receptor antagonism during restraint stress did not prevent the reduction of withdrawal 7 days later.

**Experiment 4: Role of Glucocorticoid Receptors in the Interaction Between Stress and Opiate Withdrawal**

The mean (± SEM) number of withdrawal signs observed on test is shown in Figure 4. From inspection, it can be seen that withdrawal from morphine was enhanced when it was precipitated 1 day after restraint but was reduced when it occurred 7 days after restraint. Injection of the glucocorticoid receptor antagonist RU486 prior to restraint stress appeared to abolish the enhancement of opiate withdrawal observed 1 day after restraint but left unaffected the reduction in opiate withdrawal observed 7 days after restraint. The statistical analysis confirmed these observations. There was a significant increase in the number of withdrawal signs observed among the 1 day–saline group as compared with the control group, \( F(1, 30) = 4.8, p < .05 \), but a significant decrease in the number of withdrawal signs observed among the 7 days–saline group as compared with the control group, \( F(1, 30) = 7.9, p < .05 \). There was also a significant decrease in the number of withdrawal signs observed among the 1 day–RU486 group as compared with the 1 day–saline group, \( F(1, 30) = 7.7, p < .05 \). Thus, glucocorticoid receptor antagonism during restraint stress prevented the enhancement of withdrawal 1 day later. There was, however, no significant difference in the number of withdrawal signs observed among the 7 days–RU486 group as compared with the 7 days–saline group, \( F(1, 30) < 1, p < .05 \). Thus, glucocorticoid receptor antagonism during restraint stress did not prevent the reduction of withdrawal 7 days later.
Experiment 5: Effects of MK801 and RU486 on Expression of Opiate Withdrawal

The mean (+ SEM) number of withdrawal signs observed on test is shown in Figure 5. From inspection, it can be seen that injection of either MK801 or RU486 24 hr prior to withdrawal failed to alter opiate withdrawal. There was no significant difference in withdrawal between rats injected with MK801 versus saline 1 day prior to test, F(1, 28) < 1, p > .05. There was also no significant difference in withdrawal between rats injected with RU486 versus vehicle 1 day prior to test, F(1, 28) < 1, p > .05. Together these results show that the effects of MK801 and RU486 are specific to preventing the enhancement of withdrawal by restraint stress.

Discussion

Injection of naloxone among morphine-treated animals precipitated an acute opiate withdrawal syndrome characterized predominantly by teeth chattering, whole body or head shakes, genital grooming, and postural abnormalities. This withdrawal syndrome was specific to the interaction between naloxone and morphine because it was not observed in animals injected with naloxone but not injected with morphine. Acute opiate withdrawal was significantly enhanced by a 2-hr period of restraint stress when that stress occurred 1 day prior to opiate withdrawal. This enhancement was selective to an interaction between stress and opiate withdrawal because it was not observed among rats subject to a 2-hr period of restraint stress and injected 1 day later with saline followed by naloxone. These results show that prior exposure to stress can increase the severity of opiate withdrawal. The present results are consistent with the results of Williams et al. (1984), who showed that prior exposures to inescapable tailshock increased the severity of opiate withdrawal. Moreover, the present results are also consistent with the large body of literature showing that exposure to stress typically increases the behavioral and neurobiological effects of drugs of abuse (Lu et al., 2003). It is interesting to note that the present results show that an increase in the behavioral effects of drugs of abuse is not an inevitable consequence of prior to exposure to stress. The results of Experiment 2 revealed no change in opiate withdrawal when withdrawal was precipitated 3 days after restraint stress. More important, the results of Experiments 2–4 consistently showed that opiate withdrawal was significantly reduced by a 2-hr period of restraint stress when that withdrawal was precipitated 7 days after restraint. This ability of a brief episode of restraint stress to exert long-lasting (up to 7 days) effects on responding to opiates is surprising and to the best of our knowledge is the first demonstration that an environmental event can decrease the severity of opiate withdrawal.

These interactions between stress and opiate withdrawal were mediated, at least in part, by excitatory amino-acid and glucocorticoid receptors because administrations of either MK801 or RU486 prior to restraint stress prevented the facilitation of opiate withdrawal observed 1 day later. There was no evidence here that MK801 or RU486 prevented the stress-induced enhancement of opiate withdrawal because they had some long-lasting (i.e., 24 hr) nonspecific effect on the behavioral expression of acute withdrawal. The results of Experiment 5 showed that injection of MK801 or RU486 24 hr prior to acute withdrawal had no effect on the severity of withdrawal. This finding is consistent with prior work showing that MK801 at the dose used here does not disrupt the expression of withdrawal from chronic morphine (Trujillo & Akil, 1991). Rather, our results indicate that MK801 and RU486 acted selectively to prevent the enhancement of withdrawal by restraint stress. Thus, the present experiments show that activation of NMDA and glucocorticoid receptors during restraint stress is critical for the ability of that restraint stress to enhance opiate withdrawal. This role of NMDA and glucocorticoid receptors in determining the interaction between stress and opiates is consistent with demonstrations that these receptors mediate the effects of stress and opiates on other behavioral and neuronal responses (e.g., Lu et al., 2003; Saal et al., 2003). It is interesting to note that the reduction in withdrawal severity 7 days after restraint stress was unaffected by either NMDA or glucocorticoid receptor antagonism. This finding was surprising and indicates a dissociation in the mechanisms for stress-induced increases and decreases in opiate withdrawal severity. The mechanisms for this 7-day reduction in sensitivity to acute opiate withdrawal as well as a full characterization of the time course of stress-withdrawal interactions warrant further investigation.

Together, these findings indicate an important, but complex, interaction between stress and opiate withdrawal so that stress increases vulnerability to opiate withdrawal in the short-term via NMDA and glucocorticoid receptor-dependent mechanisms but reduces the severity of opiate withdrawal in the long-term via different mechanisms. It is not immediately clear why the same event (restraint stress) should both facilitate and inhibit opiate withdrawal. One possibility is that these interactions represent the operation of nonassociative forms of learning—namely, sensitization and habituation. That is, how the animal responds to one biologically significant event at Time 2 (e.g., withdrawal from a drug of abuse) is influenced by both feedforward (e.g., sensitization) and feedback (e.g., habituation) mechanisms from other biologically significant events experienced previously at Time 1. The present data could be interpreted to mean that restraint stress produces a short-term sensitization of opiate withdrawal via NMDA and glucocorticoid mechanisms and a long-term habituation of opiate withdrawal via different mechanisms. Irrespective of the fate of this line of reasoning regarding the roles of habituation

![Figure 5](attachment:image.jpg)

Figure 5. N-methyl-D-aspartate and glucocorticoid receptor antagonists did not modulate opiate withdrawal in the absence of stress. Rats were injected with saline, dimethyl sulfoxide (vehicle), MK801, or RU486 24 hr prior to receiving an injection of morphine (15 mg/kg) followed by an injection of naloxone (5 mg/kg). Pretreatment with MK801 or RU486 did not alter opiate withdrawal.
and sensitization in interactions between stressors and drugs of abuse, the present data show that these interactions extend beyond drug reward and highlight the need for models of these interactions that also extend beyond drug reward.

Although the present experiments document important roles for NMDA and glucocorticoid receptors in stress-withdrawal interactions, other neurotransmitter and neupeptide systems are also likely to be important. Of particular interest are the endogenous opioid peptides and their receptors (for review, see McNally & Akil, 2002a). It is well documented that exposure to restraint alters the endogenous opioid system. This stress-induced activation of the endogenous opioid system could have important implications for responsivity to exogenous opiates in the hours to days that follow, which might contribute to altered vulnerability to withdrawal. For example, Adams, Andrews, Hiller, Simon, and Holtzmann (1987) showed that a single 60-min exposure to restraint reduced sensitivity to morphine 24 hr later and that this reduction in sensitivity could be prevented by antagonism of opioid receptors prior to restraint. Consistent with a role for stress-induced activity in the opioid system altering subsequent withdrawal, Williams et al. (1984) showed that facilitation of opiate withdrawal by inescapable stress was prevented if rats were pretreated with naloxone prior to stress. However, it should be noted that dose of naloxone used in this experiment (14 mg/kg) was high and likely to have nonopioid effects. The role of the endogenous opioids in the altered vulnerability to withdrawal observed here warrants further investigation.

Finally, it is worth emphasizing that the present experiments studied withdrawal from a single injection of morphine. Antagonist-precipitated withdrawal from a single exposure to opiates has been reported in humans (e.g., Heishman, Stitzer, Bigelow, & Liebson, 1989) and other animals. In rats, this acute withdrawal syndrome has been indexed by somatic signs of withdrawal (e.g., Williams et al., 1984), conditioned place aversions (e.g., Azar, Jones, & Schulteis, 2003), conditioned taste aversion (e.g., McDonald, Parker, & Siegel, 1997), and increases in pain sensitivity (hyperalgesia) (Kim, Fields, & Barbaro, 1990). However, because we studied acute opiate withdrawal in these experiments, it follows that the role of NMDA and glucocorticoid receptors in interactions between stress and withdrawal from chronically administered morphine remains unknown. It was necessary to study withdrawal from acutely administered morphine in these experiments because a history of opiate exposures themselves increases vulnerability to restraint stress (Blatchford et al., in press). It is not possible, therefore, to assess interactions between stress and opiate withdrawal in opiate-experienced animals unconfounded by this vulnerability. However, the present results, taken in combination with previous results (Blatchford et al., in press), document a bidirectional interaction between stress and opiates. A history of opiate exposures increases vulnerability to stress, and a history of stress increases vulnerability to opiate withdrawal. This bidirectional interaction between responding to opiates and stress may offer novel insights into the behavioral and neural adaptations underpinning drug abuse.

References


