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Continuous administration of opioids produces locomotor sensitization

Keith A. Trujillo*, Kate S. Kubota, Kathleen P. Warmoth

Department of Psychology and Office for Biomedical Research and Training, California State University San Marcos, San Marcos, CA 92096, United States

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Abstract

Sensitization, a behavioral phenomenon characterized by an escalating pattern of drug response following repeated administration, is thought to be involved in the development of addiction. Research on certain drugs of abuse, most notably the psychomotor stimulants amphetamine and cocaine, suggests that two factors are important to the development of sensitization: (1) drugs must be administered intermittently, rather than continuously, and (2) drugs must be administered in association with specific environmental cues. The present studies were performed to determine if the same requirements exist for opioid sensitization. If sensitization occurs following continuous infusion of the drugs, then neither intermittent administration nor specific environmental cues can be critical. Morphine was administered continuously with pellets (2×75 mg) or osmotic pumps (20 mg/kg/day), and fentanyl was administered continuously with osmotic pumps (0.2 mg/kg/day) to male Sprague–Dawley rats. Continuous infusion of either morphine or fentanyl led to an escalating pattern of activity that is characteristic of sensitization to the locomotor effects of the drugs. The escalation of activity was evident across different measures of activity, and persisted beyond continuous administration. The results suggest that, unlike sensitization to cocaine or amphetamine, intermittent administration and environmental specificity are not critical to opioid sensitization. These findings may have implications for the treatment of pain and addiction.

Keywords: Opioid; Sensitization; Locomotor; Tolerance; Analgesia; Addiction

1. Introduction

Sensitization is a behavioral phenomenon associated with repeated administration of drugs of abuse. Sometimes referred to as "reverse tolerance," sensitization represents an increase in an effect of a drug following repeated administration. Current theories suggest that sensitization is important in drug abuse, and may be responsible for the development of craving in addicts. According to this idea, repeated administration of a drug leads to an increase in desire for the drug that is the hallmark of addiction (Berke and Hyman, 2000; Kalivas et al., 1998; Koob and Le Moal, 2001; Nestler and Aghajanian, 1997; Robinson and Berridge, 1993, 2001, 2002). In addition to addiction, sensitization may be involved in the development of drug side effects. For example, the psychosis that arises from repeated administration of cocaine or amphetamine is thought to result from sensitization (Robinson and Becker, 1986). A better understanding of sensitization may therefore lead to a better understanding of drug abuse and addiction, as well as the emergence of certain drug side effects.

It is generally believed that two experimental factors are important to the development of sensitization: (1) drug administration must be intermittent rather than continuous; and (2) drug administration must occur in the presence of specific environmental cues (for reviews, see (Robinson and Becker, 1986; Stewart and Badiani, 1993). These ideas have arisen primarily from research on psychomotor stimulants. With regard to intermittency, studies have shown that repeated administration of cocaine or amphetamine produces sensitization to the locomotor stimulant effects of these drugs, while continuous administration produces tolerance (Izenwasser and French, 2002; King et

* Corresponding author. Tel.: +1 760 750 4183; fax: +1 760 750 3418.
E-mail address: keith@csusm.edu (K.A. Trujillo).

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al., 1994a,b; Kunko et al., 1998; Nelson and Ellison, 1978; Nielsen, 1981; Post, 1980; Reith et al., 1987; Robinson and Becker, 1986). With regard to environmental dependence, studies have shown that robust sensitization occurs when drug administration is associated with a specific environmental context, but does not occur (or occurs less readily) when administration is not associated with such a context (Badiani et al., 2000; Carey and Gui, 1998; Crombag et al., 2000; Robinson et al., 1998; Wolf, 1998). In fact, some researchers suggest that sensitization represents a conditioning phenomenon that is largely dependent on learned interactions between drug effects and environmental cues (Anagnostaras et al., 2002; Berke and Hyman, 2000; Carey and Gui, 1998; Pert et al., 1990; Robinson et al., 1998; Stewart and Vezina, 1988; Stewart and Badiani, 1993).

The overwhelming majority of research on sensitization has been performed on cocaine and amphetamine. Although it is generally assumed that the same principles learned from research on these psychomotor stimulants apply to sensitization to opioids and other drugs of abuse, in many cases, the research has not yet been performed. The present research explored the effects of chronic infusion of the opioids, morphine and fentanyl, on the locomotor effects of the drugs. If intermittent administration and environmental cues are critical to the development of opioid sensitization, then chronic infusion should not result in sensitization. To date, there have been only a handful of studies that have examined the potential for sensitization following continuous administration of morphine, some that found evidence of this phenomenon (Khallouk-Bousselmame and Costentin, 1994; Pollock and Kornetsky, 1996; Melchiorri et al., 1992) and others that did not (Kunko et al., 1998). The present studies extend this work by examining two different opiates (morphine and fentanyl), with morphine administered via two different approaches (pellets and osmotic pumps).

2. Materials and methods

2.1. Subjects

Adult male Sprague–Dawley rats (approx. 225–250 g at purchase; Harlan San Diego) were used in all studies. Animals were housed two per cage, in standard plastic rat cages, with food and water available ad libitum. A 12-h light/dark cycle was maintained. Animals were allowed to acclimate to the vivarium for at least 1 week prior to surgery. All experiments were conducted during the light cycle. The experimental protocol was approved by the CSU San Marcos Institutional Animal Care and Use Committee (IACUC), and is in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Apparatus

2.2.1. Analgesia

An IITC Model 33 Tail Flick apparatus was used to assess tail-flick latencies (D'Amour and Smith, 1941). Methods were similar to those used previously (Trujillo and Akil, 1991, 1994). Briefly, rats were gently restrained by hand for tail-flick tests. Three tests in a row, 10–20 s apart, were performed for each animal, and the average used in data analysis. The heat was focused 2.5–5 cm from the tip of the tail, at a different location for each of the three tests. The heat intensity was set so that baseline latencies averaged 3–5 s. A cutoff latency of 8–10 s was used to prevent tissue damage.

2.2.2. Locomotion

A Hamilton-Kinder Open Field Motor Monitor System was used to assess locomotor activity. This system consists of eight Plexiglas enclosures (16×16×15 in.). Each enclosure has two arrays of photocells (16 in each dimension): the first array is placed 5 cm above the floor and is used to measure horizontal activity; the second is 12.5 cm above the floor to measure vertical (rearing) activity. The enclosures are interfaced with a personal computer for the collection of data. The computer collects photocell beam breaks (basic movements) and calculates ambulations (interruptions of successive photocell beams leading to displacement of the animal horizontally, typically associated with forward movement), distance traveled, time at rest, fine movements (interruptions of single photocell beams, typically associated short repetitive movements) and rearing. "Basic movements" represents the broadest measure of activity; ambulations and distance traveled represent forward locomotion; fine movements represents short, repetitive movements (such as stereotypies); and rearing represents vertical activity.

2.3. Drugs and surgery

Morphine pellets (75 mg), placebo pellets and morphine sulfate were generous gifts from the National Institute on Drug Abuse Drug Supply Program. For pump studies and for challenge injections, drugs were dissolved in 0.9% saline. For challenge injections, drugs were administered in a volume of 1 ml/kg.

Pellets or osmotic minipumps (Model 2ML1, Alzet) were implanted subcutaneously under brief isoflurane anesthesia in a manner similar to that described previously (Gutstein and Trujillo, 1993; Trujillo and Akil, 1994). Briefly, a small incision was made between the shoulder blades, the pellets or pumps were inserted, and the wound closed with surgical staples. In Experiment 2, after 7 days of treatment, animals were again briefly anesthetized and pellets removed. For pellet studies, two morphine or two placebo pellets were implanted. For pump studies, each pump dispensed saline, morphine (20 mg/kg/day) or fentanyl (0.2 mg/kg/day) at a

rate of 10 μl/h (http://www.alzet.com). In order to assure that pumps were dispensing immediately upon implant, they were "primed" according to instructions from Alzet, and similar to those used previously (Gutstein and Trujillo, 1993; Trujillo and Akil, 1994). Briefly, pumps were filled the afternoon prior to the next day's surgery, placed into a saline-filled tube and incubated at room temperature overnight. One hour prior to surgery, the tubes with the pumps were placed in a 37°C water bath.

2.4. Procedures

Four experiments were performed. For all experiments, on test days during opioid infusion animals were habituated to the locomotor testing room for 30 min and then placed directly into the locomotor apparatus; activity was then assessed for 45 min (Experiment 1) or 1 h (Experiments 2, 3 and 4). Analgesia was assessed before testing for locomotor activity in Experiment 1, and after testing for locomotor activity in Experiments 2, 3 and 4.

Experiment 1 examined behaviors following morphine pellet or placebo pellet implantation across days (days 1, 3, 5 and 7 postsurgery). A follow-up study (Experiment 2) utilized the same approach, comparing morphine-pelleted with placebo-pelleted animals, however, this study focused on whether or not the increased response to morphine persisted following termination of continuous treatment. After 7 days of treatment, pellets were removed and the

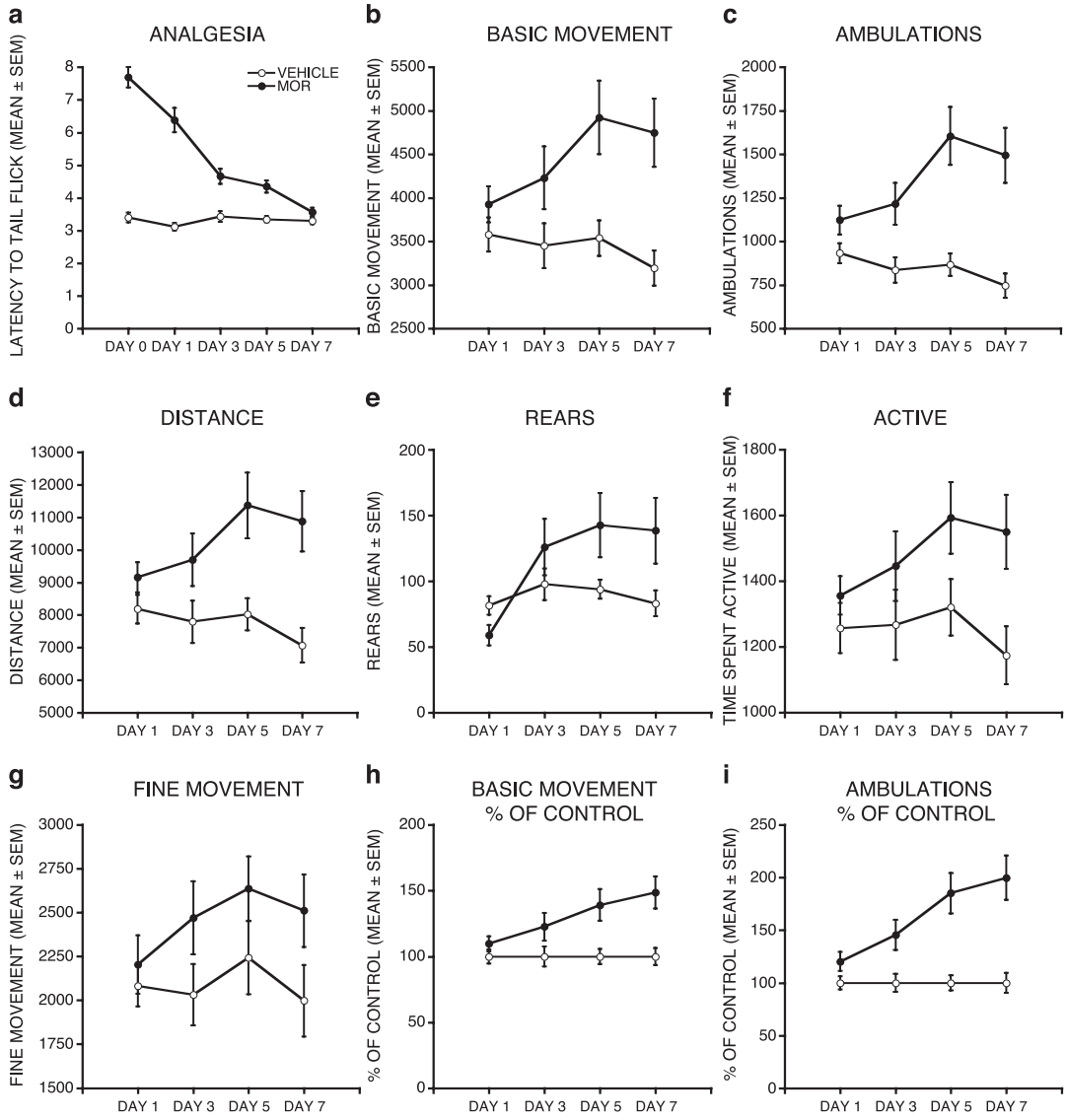

Fig. 1. Chronic administration of morphine via subcutaneous pellets (2×75 mg) produces tolerance to the analgesic effect and sensitization to the locomotor stimulant effect. (a) Analgesia (mean tail-flick latency±S.E.M.); (b) basic movements (mean counts±S.E.M.); (c) ambulations (mean counts±S.E.M.); (d) distance traveled (cm±S.E.M.); (e) rearing (mean counts±S.E.M.); (f) time spent active (s±S.E.M.); (g) fine movements (mean±S.E.M.); (h) basic movements expressed as percent of placebo control (mean±S.E.M.); (i) ambulations expressed as percent of placebo control (mean±S.E.M.). *N*=14 placebo- and 12 morphine-treated animals. Day 0=analgesic score 4 h after implant. Day 1=data following one complete day (24 h) of treatment.

animals were returned to their home cages. On the following day, animals were brought to the testing room and allowed to habituate to the room for 30 min. They were then placed in the locomotor apparatus for 30 min, injected with morphine (5 mg/kg sc) and placed back into the locomotor apparatus for an additional 210 min.

Experiment 3 examined behaviors following morphine (20 mg/kg/day) or saline administration via osmotic pumps, in order to determine if sensitization to morphine would occur following another mode of continuous administration. As in Experiment 1, activity was assessed across days of treatment (days 1, 3, 5 and 7 postsurgery). The dose of morphine was selected to approximate the daily dose administered in previous studies of opiate tolerance, dependence and sensitization (Trujillo and Akil, 1991, 1994).

In order to determine if sensitization would occur following administration of another opiate, Experiment 4 examined the effects of fentanyl (0.2 mg/kg/day) or saline administered via osmotic pumps. In this study, testing was performed on days 1 and 6 postsurgery. The dose of fentanyl was selected based on pilot studies to approximate the behavioral effects of the dose of morphine used in Experiment 3.

2.5. Data analysis

In the experiments in which the effects of the opioids were assessed across days, the data were analyzed by two-way repeated-measures ANOVA [Treatment (control vs. opioid)×Days of treatment]. Post hoc analyses (Student's *t* test) compared the treatment groups on day 1 of treatment and on the final day of chronic treatment. Basic movements were selected for statistical analysis since they represent total photocell counts, the most global measure of activity, and ambulations were selected since they represent the best measure of horizontal locomotion. Other measures are shown to illustrate the effects across different types of activity. Data analysis focused on the final 45 min of each testing session, since this is where maximal differences between groups were observed (after animals habituated to the locomotor testing enclosures each day). For the morphine challenge data in Experiment 2, total activity counts were summed for first 2 h post-injection, and a Student's *t* test was used to compare morphine and placebo groups.

3. Results

3.1. Experiment 1: Chronic administration of morphine via subcutaneous pellets produces tolerance to the analgesic effect and sensitization to the locomotor stimulant effect

Animals implanted with placebo pellets showed low baseline levels of pain responsiveness throughout testing. In contrast, animals that received chronic infusion of morphine via pellets showed maximal analgesia 4 h following implant (day 0), and this diminished dramatically over the next 2–3 days (Fig. 1a). These results demonstrate the rapid development of tolerance to the analgesic effect of morphine administered with subcutaneous pellets, as reported previously (Gold et al., 1994; Gutstein and Trujillo, 1993; Trujillo and Akil, 1994; Yoburn et al., 1985).

In activity tests, morphine-treated animals showed no differences from placebo-treated animals on the first day postsurgery. However, locomotor activity in the morphine-treated animals escalated across days, peaking at 5–7 days postsurgery. In contrast, locomotor activity in the placebo-treated animals showed a modest decline across days, consistent with mild habituation to the locomotor testing apparatus. Repeated-measures ANOVA revealed significant effects for basic movements [treatment: $F(1,24)=8.875$, $p<0.01$; time: $F(3,24)=2.80$, $p<0.05$; Time×Treatment: $F(3,72)=4.98$, $p<0.005$] and for ambulations [treatment: $F(1,24)=18.84$, $p<0.0005$; time: $F(3,24)=4.37$, $p<0.01$; Time×Treatment: $F(3,72)=8.36$, $p<0.0001$]. Post hoc *t* tests revealed no significant differences on day 1, but significant differences between groups on day 7 for basic movements [day 1: $t(24)=1.22$, n.s.; day 7: $t(24)=3.67$, $p<0.002$] and ambulations [day 1: $t(24)=1.9$, n.s.; day 7: $t(24)=4.55$, $p<0.0001$]. Similar effects were seen across other locomotor measures, including distance traveled, rearing, time spent active and fine movements (Fig. 1). The magnitude of the

Table 1
Percent increase in locomotor behavior in response to chronic treatment with morphine or fentanyl*

Experiment	Basic movements	Ambulations	Distance traveled	Rearing	Time spent active	Fine movements
Experiment 1						
Morphine pellets (2×75 mg)	49%	100%	54%	67%	32%	26%
Experiment 3						
Morphine pumps (20 mg/kg/day)	73%	148%	75%	94%	50%	72%
Experiment 4						
Fentanyl pumps (0.2 mg/kg/day)	45%	68%	52%	129%	52%	59%

* Percent increase calculated as the increase above the respective control group on the final day of testing (day 7 for Experiments 1 and 3, or day 6 for Experiment 3).

increase in activity depended on the specific locomotor measure, and ranged from a 26% increase above placebo (time active) to a 99% increase (ambulations) (Table 1). These results demonstrate that sensitization to the locomotor effects of morphine arises from continuous infusion of the drug.

3.2. Experiment 2: Sensitization produced by chronic administration of morphine persists beyond chronic treatment, as reflected by a morphine challenge

As in Experiment 1, morphine-treated animals showed an increase in activity following continuous morphine administration with pellets (data not shown). When challenged with morphine one day following removal of pellets, animals that previously received placebo showed a modest increase in activity, reflective of the stimulant effect of this dose of morphine. Animals that previously received morphine showed a more potent stimulant effect that lasted throughout the testing session (Fig. 2). Statistical analysis revealed a significant difference between morphine- and placebo-treated animals for basic movements [$t(9)=2.4$, $p<0.05$], and an effect that approached significance for ambulations [$t(9)=2.03$, $p=0.07$]. Similar effects were seen across other locomotor measures, including distance traveled, rearing, time spent active and fine movements (data not shown). These results demonstrate that the sensitizing effect of chronic morphine is not restricted to the duration of infusion, but persists after termination of chronic treatment.

3.3. Experiment 3: Chronic administration of morphine via osmotic pumps produces sensitization to the locomotor stimulant effect

Animals that received chronic infusion of morphine via pumps showed no difference from placebo-treated animals on the first day postsurgery. However, locomotor activity in the placebo-treated animals showed a decline across days, consistent with habituation to the locomotor testing apparatus. In contrast, locomotor activity in the morphine-treated animals did not change across days, resulting in an increase in activity relative to controls over time. This is best seen when the data are converted to percent of control (Fig. 3). Repeated-measures ANOVA revealed significant effects for ambulations [treatment: $F(1,8)=7.83$, $p<0.05$; time: $F(3,8)=3.06$, $p<0.05$; Time×Treatment: $F(3,24)=0.396$, n.s.], but not for basic movements [treatment: $F(1,8)=3.28$, $p=0.11$; time: $F(3,8)=1.98$, n.s.; Time×Treatment: $F(3,24)=0.66$, n.s.]. Post hoc t tests revealed no difference between groups on day 1 of treatment, but significant differences by day 7 for both basic movements [day 1: $t(8)=0.62$, n.s.; day 7: $t(8)=2.43$, $p<0.05$] and ambulations [day 1: $t(8)=1.21$, n.s.; day 7: $t(8)=3.38$, $p<0.01$]. Similar effects were seen across locomotor measures, including distance traveled, rearing, time spent active and fine movements. The magnitude of the increase in activity depended on the specific locomotor measure, and ranged from a 50% increase above placebo (time active) to a 148% increase (ambulations) (see Table 1). These results suggest that sensitization following continuous infusion of morphine occurs following different modes of administration, including both pellets and osmotic pumps.

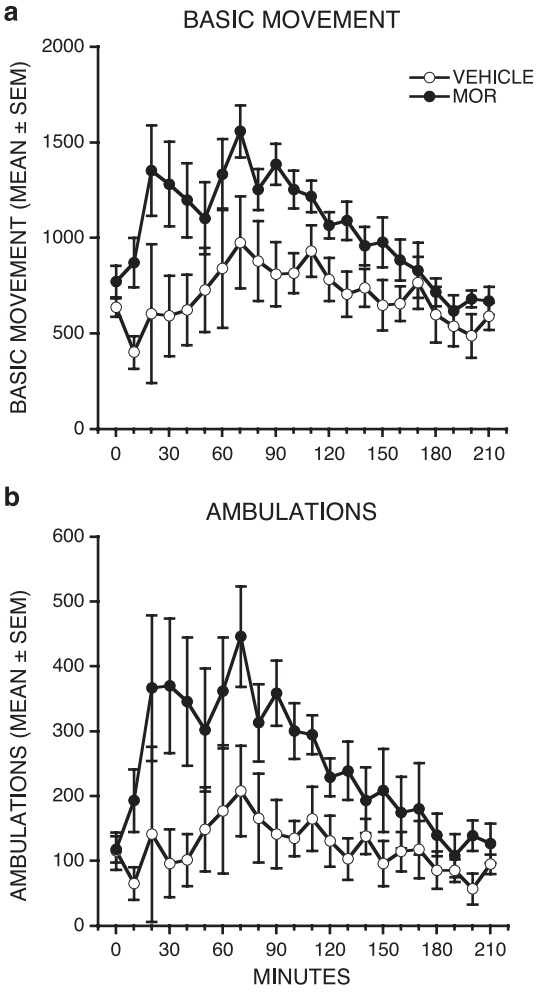

Fig. 2. Sensitization produced by chronic administration of morphine (2×75 mg pellets) persists beyond chronic treatment. Animals were implanted with either placebo or morphine pellets, and the pellets were removed on day 7 after implantation. Morphine (5.0 mg/kg) challenge was administered the following day to both groups and locomotor activity was assessed. Data represent the time-course of the morphine response in animals previously exposed to morphine (MOR) or placebo (VEHICLE). (a) Basic movements (mean counts±S.E.M.); (b) ambulations (mean counts±S.E.M.). N=4 placebo- and 7 morphine-treated animals.

3.4. Experiment 4: Chronic administration of fentanyl via osmotic pumps produces sensitization to the locomotor stimulant effect

To examine whether another opiate would produce sensitization, osmotic pumps were used to administer

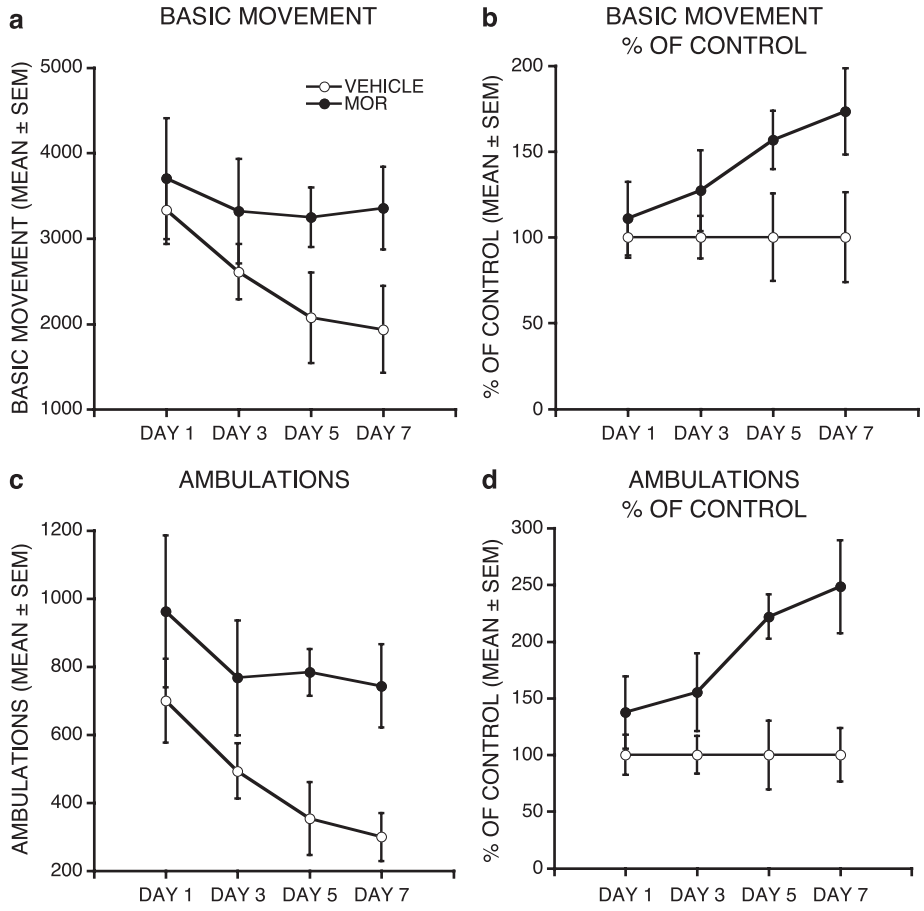

Fig. 3. Chronic administration of morphine (MOR; 20 mg/kg/day) via osmotic pumps produces sensitization. (a) Basic movements (mean counts±S.E.M.); (b) basic movements expressed as percent of saline (VEHICLE) control (mean±S.E.M.); (c) ambulations (mean counts±S.E.M.); (d) ambulations expressed as percent of saline control (mean±S.E.M.). *N*=5 morphine- and 5 saline-treated animals.

fentanyl (Fig. 4). Animals that received chronic infusion of fentanyl via pumps showed no differences from saline-treated animals on the first day postsurgery, but did show increases following 6 days of treatment. While saline-treated animals showed no change in behavior across days, fentanyl-treated animals showed an escalation in locomotor activity. Repeated-measures ANOVA revealed effects of treatment that approached significance for basic movements [treatment: $F(1,12)=3.95$, $p=0.07$; time: $F(1,12)=1.92$, n.s.; Time×Treatment: $F(1,12)=2.64$, n.s.] and for ambulations [treatment: $F(1,12)=4.27$, $p=0.06$; time: $F(1,12)=.12$, n.s.; Time×Treatment: $F(1,12)=1.55$, n.s.]. Post hoc t tests revealed no difference between groups on day 1 of treatment, but significant differences by day 6 for both basic movements [day 1: $t(12)=0.44$, n.s.; day 6: $t(12)=3.39$, $p<0.006$] and ambulations [day 1: $t(12)=0.68$, n.s.; day 6: $t(12)=3.87$, $p<0.005$]. Similar effects were seen across other locomotor measures, including distance traveled, rearing, time spent active and fine movements. The magnitude of the increase in activity depended on the specific locomotor measure, and ranged from a 45% increase above placebo (basic movements) to a 129% increase (rearing) (see Table 1). These data demonstrate that sensitization occurs following chronic infusion of fentanyl, as well as morphine.

4. Discussion

To summarize the key findings of these studies, continuous administration of morphine or fentanyl produced an escalating pattern of activity across days of administration. This escalating pattern was seen across locomotor measures, including basic movements (raw photocell counts), horizontal activity (ambulations and distance traveled), vertical activity (rearing), fine movements and time spent active. These results provide evidence of sensitization following continuous administration of opioids, supporting and extending previous work by others (Khallouk-Bousselmame and Costentin, 1994; Pollock and Kornetsky, 1996; Melchiorri et al., 1992). Moreover, the results suggest that two factors believed by many to be critical to the development of sensitization—intermittent administration and environmental context—may not be essential, at least for opioids.

In the present studies, the escalation of locomotor activity characteristic of sensitization was accompanied by tolerance to the analgesic effect of the opiates, however, the two behavioral phenomena appeared to be dissociated in time. This is particularly evident in Experiment 1, which utilized two morphine pellets. Tolerance developed rapidly

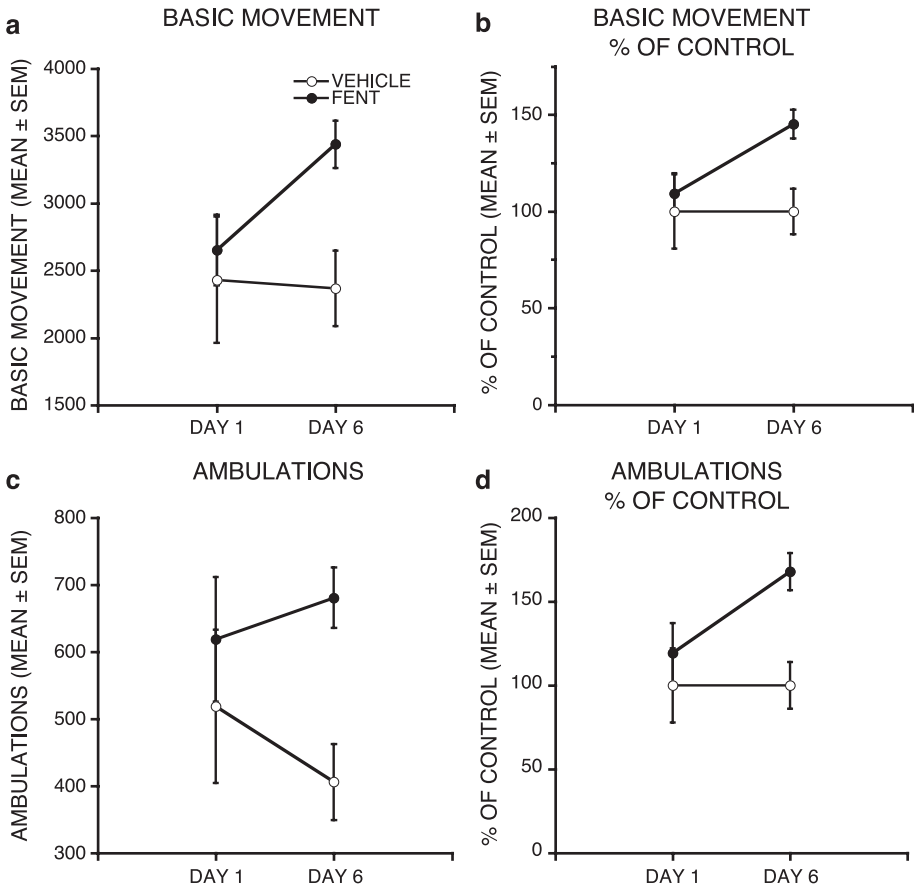

Fig. 4. Chronic administration of fentanyl (FENT; 0.2 mg/kg/day) via osmotic pumps produces sensitization. (a) Basic movements (mean counts±S.E.M.); (b) basic movements expressed as percent of saline (VEHICLE) control (mean±S.E.M.); (c) ambulations (mean counts±S.E.M.); (d) ambulations expressed as percent of saline control (mean±S.E.M.). *N*=6 saline- and 8 fentanyl-treated animals.

over the first 3 days, while sensitization escalated steadily over the 7 days of treatment. The dissociation in these effects should not be surprising, as tolerance to opiate analgesia and sensitization to opiate locomotion involve different neural systems; the former mediated largely at the spinal level (Berge and Hole, 1981; Gutstein and Trujillo, 1993), and the latter involving the mesocorticolimbic system (Kalivas et al., 1998; Vanderschuren and Kalivas, 2000; Wolf, 1998).

Previous research on cocaine and amphetamine has suggested that intermittent administration is necessary to produce sensitization. Continuous administration of these drugs leads to tolerance to the locomotor effects (Izenwasser and French, 2002; King et al., 1994a,b; Kunko et al., 1998; Nelson and Ellison, 1978; Nielsen, 1981; Post, 1980; Reith et al., 1987; Robinson and Becker, 1986) (or a transient increase in activity, evident on the second day of administration, followed by loss of the sensitization (Izenwasser et al., 1999; Izenwasser and French, 2002; Johansson et al., 1992; Kunko et al., 1998)). On the other hand, very little work has explored the ability of continuous administration of opioids to produce sensitization. There have been two previous studies, similar to our Experiment 2, that examined the effects of a challenge dose of morphine after a delay following continuous infusion, one that showed increased locomotor activity (Khallouk-Bousselmame and Costentin, 1994), and another that showed enhanced oral stereotypy (Pollock and Kornetsky, 1996). These studies are therefore consistent with the suggestion that continuous infusion of morphine can produce sensitization to certain behavioral effects.

There have also been two previous studies, similar to our Experiment 3, which followed locomotor activity across days of morphine administration with osmotic pumps, one that found evidence of sensitization (Melchiorri et al., 1992) and the other that did not (Kunko et al., 1998). Melchiorri et al. (1992) observed increases in both distance traveled and rearing over 9 days of administration of morphine (12 mg/kg/day), providing support for sensitization. In contrast, Kunko et al. (1998) found no changes in horizontal activity over 7 days of morphine administration (15 mg/kg/day). It should be noted that the latter finding is somewhat similar to our Experiment 3, in which we administered morphine by osmotic pumps (20 mg/kg/day). As in this previous study, in our experiment the locomotor effect of morphine showed no significant change across days. A key difference, however, is that in our study the saline control group showed significant habituation. The

morphine group was therefore sensitized relative to the control group in our experiment. The potential sensitization in our Experiment 3 is particularly evident when the locomotor activity is expressed as a percent of control (see Fig. 3b,d and Table 1). An alternative explanation is that in this experiment, sensitization did not develop, but instead morphine inhibited the development of habituation. However, given the findings in the other experiments, in which overt sensitization was observed, we believe that a better interpretation for these results is that sensitization to the locomotor effect of morphine developed, but that it was countered by a concurrent habituation to the locomotor testing situation. The differences in the pattern of habituation and sensitization between Experiments 1 and 3 may be due to differences in dosing, differences in drug availability between pellets and pumps or differences in the duration of locomotor testing on each day (45 min in Experiment 1 vs. 1 h in Experiment 3). Alternatively or additionally, physical differences in size and shape of the pellets and the pumps may have contributed, since the pumps are considerably bulkier than the pellets. However, this is speculation—parametric studies examining these and other potential factors are needed to conclusively determine the reasons for the differences in the present studies.

It might be argued that intermittent administration of the opiates inadvertently occurred in the present experiments. However, earlier work has demonstrated that administration of morphine via pellet implantation results in stable plasma levels of morphine across days (Gold et al., 1994; Yoburn et al., 1985). Similarly, osmotic pumps deliver stable levels of drugs throughout the life of the pumps (see http://www.alzet.com). It is therefore unlikely that the drugs were inadvertently administered intermittently. Because animals were continuously exposed to drugs throughout the administration period, specific drug–environment interactions thought by many to be essential to the development of sensitization could not have developed. Thus, intermittent administration and environmental context do not appear to be critical to the development of morphine or fentanyl sensitization.

It needs to be mentioned that a complete dependence of sensitization on environmental context has already been ruled out for psychomotor stimulants. In an elegant series of studies, Robinson et al. (1998) demonstrated that psychomotor stimulant sensitization is not entirely dependent on drug–environment interactions; instead, environmental context dramatically shifts the dose response, allowing for the development of sensitization at lower doses of the drugs. It is unclear whether the analogous situation can be applied to intermittency (i.e. that it is not obligatory, but that it shifts the dose response for the development of sensitization). Further work, exploring multiple doses of opioids and other drugs, and various modes of administration should determine the answer to this question.

The present results, by expanding our understanding of sensitization, have implications for drug abuse and addiction, and in particular, for the development of craving (Kalivas et al., 1998; Robinson and Berridge, 1993, 2001, 2002). Additionally, because continuous administration of opioids (via patches or pumps) is utilized in the treatment of pain, the results may have implications for chronic pain patients. It is unclear if the present findings are restricted to opioids, or if they might extend to other drugs of abuse. On a related note, we should add that we have preliminary evidence that chronic infusion of another opiate, methadone, via osmotic pumps produces sensitization. Further work should explore multiple doses and treatment approaches to determine whether or not sensitization to other opioids and other drugs of abuse will occur during continuous infusion.

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