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Cardiovascular changes during morphine administration and spontaneous withdrawal in the rat

Raymond Chan *, Rodney Irvine, Jason White

Department of Clinical and Experimental Pharmacology, Medical School North, University of Adelaide, Adelaide, South Australia 5005, Australia

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Abstract

Morphine maintenance doses of 10 mg kg^{-1} day^{-1}, 20 mg kg^{-1} day^{-1} and 30 mg kg^{-1} day^{-1} were administered to three groups of rats via miniosmotic pumps for 7 days to induce physical dependence. They were then allowed to undergo spontaneous withdrawal. Radiotelemetric blood pressure measurements showed that morphine increased systolic and diastolic blood pressure on the first day of morphine treatment and produced a dose dependent decrease in heart rate, systolic and diastolic blood pressure thereafter. After the peak depressive effect, development of tolerance to morphine was observed in systolic and diastolic blood pressure, but not in the heart rate. During spontaneous withdrawal, both systolic and diastolic blood pressure increased beyond pre-morphine levels for all doses and there was a rebound increase in heart rate at the 30 mg kg^{-1} day^{-1} dose. These results suggest that the improved sensitivity of telemetric measures combined with the use of minipumps for morphine treatment provide an animal model of spontaneous opioid withdrawal.

Keywords: Morphine; Cardiovascular; Withdrawal, spontaneous; Radiotelemetry; Osmotic pump; (Rat)

1. Introduction

Physical dependence and tolerance are the well-known consequences of repeated administration of opioids such as morphine. Physical dependence is associated with a withdrawal syndrome following either the abrupt termination of morphine intake or precipitation by the administration of an opioid receptor antagonist. The opioid abstinence syndrome originally identified in humans consists of characteristic signs and symptoms including lacrimation, rhinorrhea, yawning, hyperthermia, hyperventilation (Himmelsbach, 1937). In animals, a range of morphine withdrawal signs have been explored over the last three decades (Akera and Brody, 1968; Wei et al., 1973; Tieger, 1974; Katovich et al., 1986). In particular, body weight loss, 'wet dog' shakes in the rat (Akera and Brody, 1968; Cicero and Meyer, 1973; Wei, 1973) and withdrawal jumping in the mouse (Collier et al., 1972) have been shown to be reliable indicators of withdrawal. There are drawbacks associated with the methods used in these experiments. They rely on experimenter observation, many of the measures are quantal rather than continuous and it may be difficult to assess withdrawal severity at a particular point in time.

In order to induce dependence, a variety of procedures have been used to administer morphine chronically. These included implantation of morphine pellets (Way et al., 1969; Wei et al., 1973), continuous infusion (Goode, 1971; Tieger, 1974), intermittent injections (Akera and Brody, 1968; Mucha et al., 1979) and oral administration in drinking solutions (Leander et al., 1975). More recently, osmotic pumps, which have the advantage of providing a constant rate of drug delivery, have also been used. Tolerance and dependence to opioids administered via osmotic minipump have been quantified by different behavioural responses (Adams and Holtzman, 1990; Paronis and Holtzman, 1992). Although morphine pellets are the most common way of inducing dependence, one disadvantage of this technique is that it cannot be used to study spontaneous (non-precipitated) withdrawal.

One way of assessing withdrawal severity that provides a continuum of severity that can be recorded at any point in time is through assessment of cardiovascular changes. The direct cardiovascular actions of morphine have been recognized for a long time and the post-withdrawal increase in arterial blood pressure in humans was identified

* Corresponding author. Tel.: +61-8-8303-5188; Fax: +61-8-8224-0685; E-mail: rchan@medicine.adelaide.edu.au

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early (Himmelsbach, 1937, 1942). Clinically, post-withdrawal arterial blood pressure was used as one of the major indexes to assess the severity of the opioid withdrawal syndrome (Kolb and Himmelsbach, 1938; Himmelsbach, 1942; Jasinski, 1977). In contrast, very few animal studies have investigated the cardiovascular changes during morphine withdrawal in a quantitative fashion. It has been demonstrated that measurement of the mean arterial blood pressure in unanesthetized morphine dependent rats is an objective and reliable measure of both withdrawal intensity and the degree of physical dependence. Also, the post-withdrawal increase in mean arterial blood pressure was proven to be superior as a predictor of the degree of morphine physical dependence compared to several other signs (Buccafusco, 1983; Buccafusco et al., 1984; Marshall and Buccafusco, 1985).

While antagonist-precipitated withdrawal has been most frequently assessed in studies of opioid physical dependence, spontaneous withdrawal provides a better model of withdrawal experienced by opioid dependent humans. Unfortunately, very few animal studies have measured cardiovascular changes during spontaneous opioid withdrawal. Even when such changes have been measured, the dose of morphine used has been as high as 100 mg kg^{-1} day^{-1} (Buccafusco, 1983; Marshall and Buccafusco, 1985) and no dose–response relationship has been demonstrated. In these studies, the major change observed has been mean arterial blood pressure; changes in systolic and diastolic blood pressure were not reported (Buccafusco, 1983; Marshall and Buccafusco, 1985). Heart rate, although used as an index of opioid withdrawal in humans, was reported to show no significant changes during spontaneous withdrawal in the rat (Buccafusco, 1983).

Results from studies measuring cardiovascular changes depend in part on the method used to measure such changes. Blood pressure measurement is mainly confined to the indirect tail-cuff technique and direct arterial catheterisation. However, the tail-cuff technique does not permit continuous measurement over prolonged periods, the animal needs to be restrained and the measurement errors can be quite large (Bunag et al., 1971). Chronic direct arterial catheterisation can provide a continuous measurement for long-term studies, but also requires disruption of normal behaviour and use of some restraint, with the potential for stress-induced artifact (Bunag, 1984; Brockway et al., 1991).

The development of radiotelemetry implants in the 1990s has allowed simultaneous recording of heart rate, systolic and diastolic blood pressure together with locomotor activity (Berkey et al., 1990; Brockway et al., 1991; Guiol et al., 1992; Van den Buuse, 1994) and continuous measurement over extended periods. It has the ability to detect any changes of withdrawal signs at the earliest possible point in an unrestrained animal. Recent studies have shown that unrestrained animals have a lower resting blood pressure and heart rate indicative of lower stress (Guiol et al., 1992; Bazil et al., 1993; Narvaez et al., 1993).

The present study was designed to develop an animal model of opioid effects by investigating the cardiovascular changes arising from morphine administration, the development of tolerance to these effects and the changes during spontaneous withdrawal. Morphine was administered by continuous infusion from osmotic pumps. The whole time course of changes in systolic and diastolic blood pressure, and heart rate were measured; locomotor activity was recorded during the same time period. Three relatively low doses of morphine were used to assess the dose–response relationships.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats weighing between 250 and 350 g were used in this study (ARC Animal Breeding Unit, West Australia). They were individually housed in a room with a 12–12 h light/dark cycle at a constant temperature of 23°C. Animals received standard laboratory rat chow and water ad libitum. The Animal Ethics Committee of the University of Adelaide approved all experiments.

2.2. Procedure for surgical implantation of radiotelemetric implants

Radiotelemetric devices (TA11PA-C40, Data Sciences, St. Paul, MN) were surgically implanted according to the procedure previously described (Brockway et al., 1991). In brief, rats were anesthetized with a mixture of methohexitone sodium (10 mg ml^{-1}) and pentobarbital sodium (60 mg ml^{-1}), 9:1, administered at a dose of 5 ml kg^{-1} intraperitoneally. A midline abdominal incision was made, and the telemetry devices were implanted under aseptic conditions into the peritoneal cavity. A fluid-filled sensor catheter was inserted in the descending aorta above the iliac bifurcation and fixed in places with tissue adhesive (3M, Animal Care Products, St. Paul, MN). The tip of the catheter was positioned in the abdominal aorta caudal to the renal arteries and the body of the implant was immobilized by suturing to the ventral abdominal wall. The abdomen was closed with suture clips, topical antibiotic powder applied, and systemic antibiotic (Tribrissen®) given subcutaneously. Clips were removed 5 days later and the animals allowed to recover for a further 5 days before use.

2.3. Morphine administration

Physical dependence was induced with morphine hydrochloride administered via osmotic minipumps (Alzet Model 2ML1, Alza, Palo Alto, CA), which delivered approxi-

mately 2 ml of drug solution at a constant infusion rate of 10.51 μl h^{-1} over 7 days. Osmotic pumps were prefilled with infusion solution of morphine hydrochloride at the appropriate concentration to provide the daily dose required by the experimental protocol. The pumps were incubated in physiological (0.9%) saline at 37°C for 4 h prior to implantation. Rats were anaesthetized with a mixture of halothane (2%), oxygen and nitrous oxide (2:1). The pumps were implanted subcutaneously on the dorsum of the rat and the wound closed with autoclips. After 7 days of infusion, pumps were removed under brief (2–3 min) general anaesthesia as described above and the wound resutured.

2.4. Telemetric monitoring

Individual rat cages were placed on top of receivers (RA1010, Data Sciences) for measurement of heart rate, locomotor activity, systolic and diastolic blood pressure. The data were collected with a computer programmed with LabPro software (Data Sciences). The waveform-sampling rate was set to 250 Hz with a 100 Hz filter.

2.5. Experimental protocol

2.5.1. Pretreatment period

Prior to the drug infusion period, 2 days of baseline data were collected (heart rate, systolic and diastolic blood pressure) hourly. Collection periods occurred every 10 min for a duration of 10 s.

2.5.2. Treatment period

Morphine was administered over 7 days via miniosmotic pumps at maintenance doses of 10 mg kg^{-1} day^{-1}, 20 mg kg^{-1} day^{-1} and 30 mg kg^{-1} day^{-1}, respectively in three groups of animals. Animals in the control group were given 0.9% saline in a similar manner. Data were collected daily at three different periods (4 p.m. to 7 p.m., 11 p.m. to 3 a.m. and 7 a.m. to 11 a.m.) once every 10 min for 10 s.

2.5.3. Post-treatment period

At the end of day 7, pumps were removed under brief anaesthesia using the mixture of halothane and nitrous oxide as previously described. The rats were then allowed to undergo spontaneous withdrawal. Radiotelemetry recording was conducted immediately following pump removal for 3 days. Data were collected at the same periods and for the same duration as in the treatment period.

2.6. Drugs

Morphine hydrochloride was purchased from Glaxo Australia (Victoria, Australia). Methohexitone sodium (Brietal) was purchased from Eli Lilly (Westride, NSW, Australia) and pentobarbital sodium (Nembutal) from Boehringer Ingelheim (Artarmon, NSW, Australia). The systemic antibiotic, Tribrissen® (Trimethoprism/sulfadiazine) was purchased from Jurox (Silverwater, NSW, Australia).

2.7. Data analysis

The results were expressed as mean ± S.E.M. The minimum level for statistical significance was $P < 0.05$. To analyze changes in heart rate, systolic and diastolic blood pressure during chronic administration of morphine hydrochloride, the day with the peak morphine effect and the last day of morphine infusion were compared with the baseline values, using Student's *t*-test. To analyze spontaneous withdrawal effect, the changes in heart rate, systolic and diastolic blood pressure between the baseline and the peak withdrawal day for each animal were first calculated. These were compared with the control group results by one-way analysis of variance followed by Dunnett's post hoc test.

3. Results

3.1. Chronic infusion of morphine

Fig. 1 shows the direct effect of chronic infusion of saline (control group) and morphine (treated group) on systolic and diastolic blood pressure, and heart rate in conscious unrestrained rats. There were no significant changes for systolic and diastolic blood pressure or heart rate during continuous infusion of morphine at a dose of 10 mg kg^{-1} day^{-1}. Morphine doses of 20 mg kg^{-1} day^{-1} and 30 mg kg^{-1} day^{-1} significantly decreased systolic blood pressure at a peak level by 4 mm Hg and 13 mm Hg, respectively, compared to baseline (Fig. 1a). Diastolic blood pressure decreased significantly (by 12 mm Hg) only following the 30 mg kg^{-1} day^{-1} dose (Fig. 1b). Significant changes in heart rate were observed following administration of the two higher doses: a decrease of 31 beats min^{-1} at 20 mg kg^{-1} day^{-1} and 28 beats min^{-1} at 30 mg kg^{-1} day^{-1} (Fig. 1c).

Tolerance to the cardiovascular effects of morphine is also shown in Fig. 1. There was clear evidence of tolerance to the effects of morphine on systolic and diastolic blood pressure, but not to the effects on heart rate. Systolic blood pressure increased significantly by 6 mm Hg and 8 mm Hg towards baseline values compared to the day of peak morphine effect at doses of 20 and 30 mg kg^{-1} day^{-1}, respectively (Fig. 1a). This also occurred for diastolic blood pressure at the 30 mg kg^{-1} day^{-1} dose, with an elevation of 6 mm Hg (Fig. 1b).

3.2. Time course of changes during treatment for control group and 30 mg kg^{-1} day^{-1} morphine treated group

From the above results, the most significant changes in heart rate, systolic and diastolic blood pressure were ob-

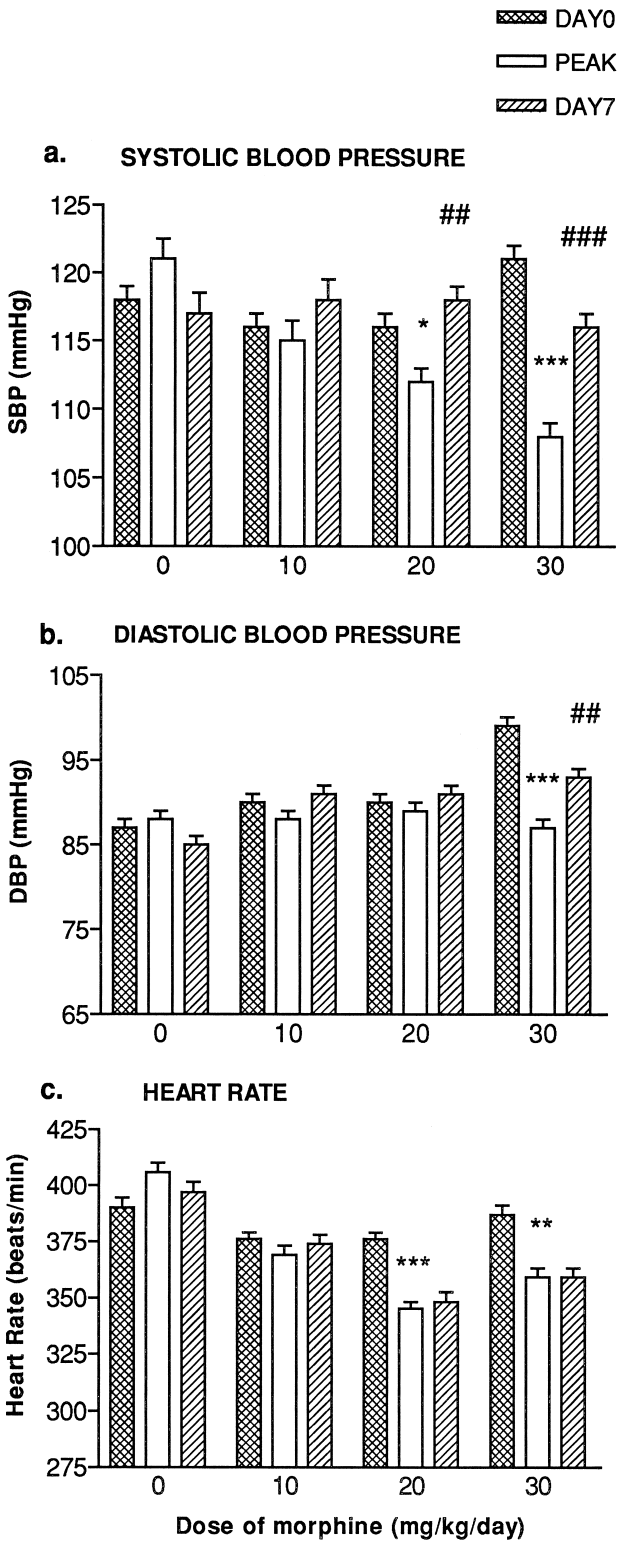

Fig. 1. Summary of the effects of chronic administration of saline (0 mg kg^{-1} day^{-1}) and three different maintenance doses of morphine (10, 20 and 30 mg kg^{-1} day^{-1}) on: (a) systolic blood pressure, (b) diastolic blood pressure, and (c) heart rate. Data are expressed as mean ± S.E.M., $n = 4$ for all groups. Peak morphine effect value was compared with the day 0 (baseline value), $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$, Student's *t*-test. The effect on the last day of drug administration (day 7) was compared with the peak morphine effect values, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$, Student's *t*-test.

served for the morphine maintenance dose of 30 mg kg^{-1} day^{-1}. Fig. 2a,b and c illustrate the respective time course of changes for systolic and diastolic blood pressure, and heart rate, during pre-treatment, morphine treatment and the post-treatment period.

The pre-treatment (day 0) value was used as the reference value for changes in heart rate, systolic and diastolic blood pressure during treatment and post-treatment periods. On day 1 (first day of morphine treatment), both systolic and diastolic blood pressure increased to levels significantly higher than those of the control group (Fig. 2a and b, respectively). Systolic and diastolic blood pressure decreased markedly on the next day and were significantly lower than the control group. Both values decreased progressively until maximal effects were reached on day 5. Following that, tolerance can be observed as gradual increases towards the baseline values. On day 7, the values for both systolic and diastolic blood pressure were not significantly different from those of the control group. In contrast to the changes in blood pressure, heart rate was significantly lower in morphine treated animals for days 2–7, with no evidence of tolerance (Fig. 2c).

3.3. Effects of spontaneous withdrawal of morphine on systolic blood pressure, diastolic blood pressure and heart rate in conscious, unrestrained rats

Fig. 3a,b and c show differences between the first day following cessation of morphine administration and the pretreatment values for systolic and diastolic blood pressure, and heart rate, respectively. These are shown for the three morphine treated groups and the control group.

For each of the three parameters there is clear evidence of a dose-related increase in withdrawal severity. Significant increases in systolic blood pressure occurred following cessation of administration of the 20 mg kg^{-1} day^{-1} dose, with much greater increases following cessation of administration of morphine at 30 mg kg^{-1} day^{-1}. Diastolic blood pressure increased significantly at all three doses, and also with much greater increase at the 30 mg kg^{-1} day^{-1}. In contrast, a statistically significant increase in heart rate was only observed in the 30 mg kg^{-1} day^{-1} morphine treated group when compared with the control group.

3.4. Time course of changes during post-treatment for control group and 30 mg kg^{-1} day^{-1} morphine treated group

Following cessation of morphine at the end of day 7, systolic and diastolic blood pressure values rebounded significantly on day 8 (first day of spontaneous withdrawal), as shown in Fig. 2a and b. Similar changes were observed in heart rate. Following these changes on the first day after treatment cessation, systolic and diastolic blood pressure, and heart rate dropped gradually towards the

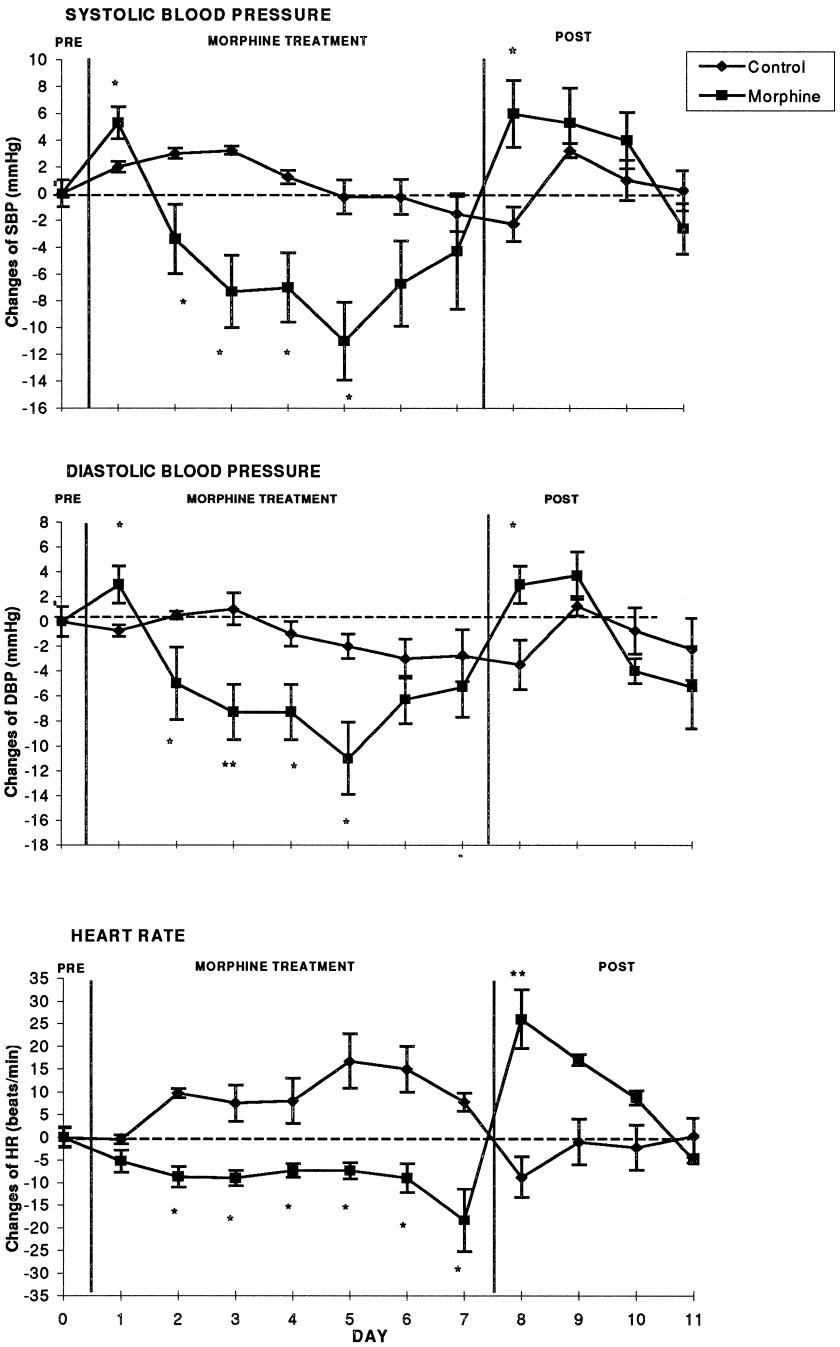

Fig. 2. Time course for: (a) systolic blood pressure, (b) diastolic blood pressure, and (c) heart rate changes during treatment and post-treatment (compared to pre-treatment value) for control group (◇) and 30 mg kg^{-1} day^{-1} morphine treated group (♦). The pre-treatment value was adjusted to zero and other values are presented either as positive (increased) or negative (decreased) relative to the pre-treatment value. Data are expressed as the mean ± S.E.M., $n = 4$, $^{*}P < 0.05$ and $^{**}P < 0.01$, Student's *t*-test.

baseline values and were not significantly different from the control group values.

3.5. Time course for locomotor activity changes during morphine treatment and withdrawal for three morphine treated groups

Locomotor activity data are shown in Fig. 4. For the 10 mg kg^{-1} day^{-1} morphine treatment group, locomotor activity counts were significantly increased on the first and second day of morphine infusion compared to values of the control group (Fig. 4a). Thereafter, locomotor activity was very similar for control and treatment groups. At the morphine maintenance dose of 20 mg kg^{-1} day^{-1} (Fig. 4b), locomotor activity counts increased significantly only on the first day of drug infusion. At 30 mg kg^{-1} day^{-1}, no significant difference in locomotor activity was observed

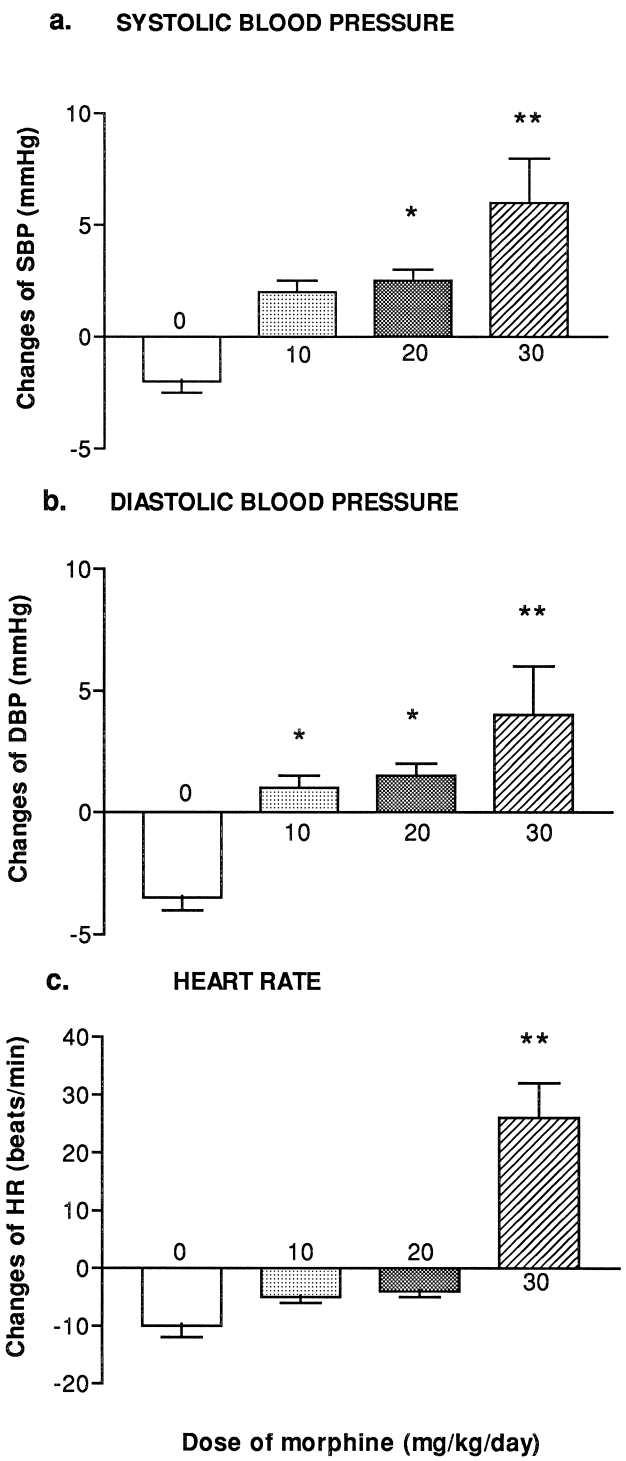

Fig. 3. Summary of spontaneous morphine withdrawal induced changes in (a) systolic blood pressure, (b) diastolic blood pressure, and (c) heart rate for the control group and groups administered morphine at maintenance doses of 10 mg kg^{-1} day^{-1}, 20 mg kg^{-1} day^{-1} and 30 mg kg^{-1} day^{-1}. Each bar represents the mean difference between pre-morphine treatment and the peak withdrawal day for systolic blood pressure, diastolic blood pressure and heart rate, respectively ($n = 4$). $^{*}P < 0.05$, $^{**}P < 0.01$, compared to control with one-way ANOVA followed by Dunnett's post hoc test.

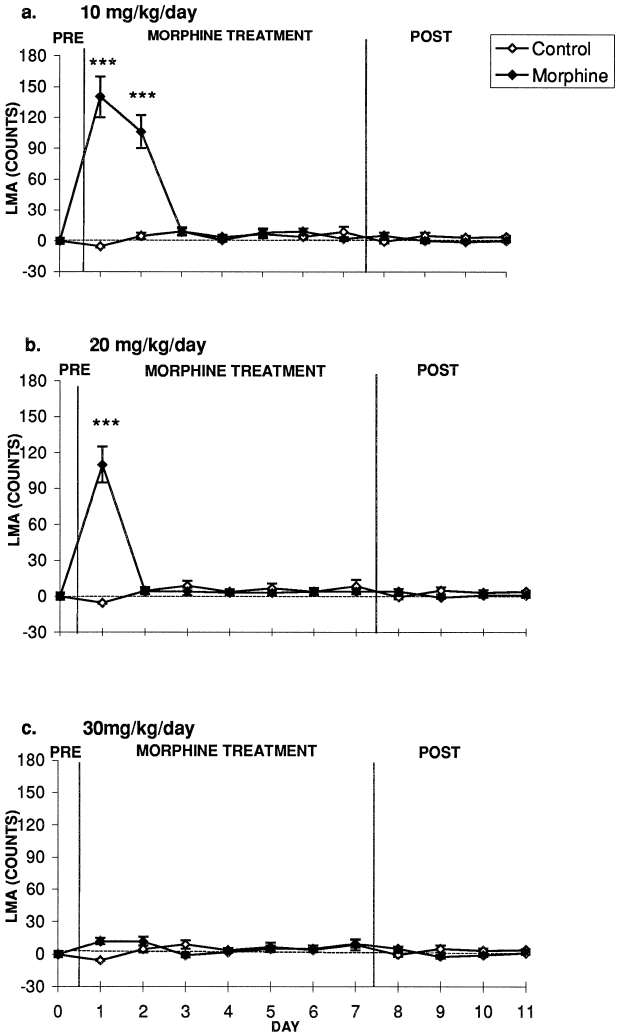

Fig. 4. Time course of changes in locomotor activity during treatment and post-treatment (compare to pre-treatment value) for: (a) 10 mg kg^{-1} day^{-1}, (b) 20 mg kg^{-1} day^{-1}, and (c) 30 mg kg^{-1} day^{-1} morphine treated groups (◇) and control group (◆). Values are presented either as positive (increased) or negative (decreased) compared to the pre-treatment value. Data are expressed as the mean ± S.E.M., $n = 4$, and $^{***}P < 0.01$, Student's t-test.

between treatment and the control groups (Fig. 4c). There were no withdrawal-induced changes in locomotor activity for any of the three morphine treated groups.

4. Discussion

The results presented in this report indicate that cardiovascular measurements such as blood pressure and heart rate can provide a means of objective and continuous assessment of opioid effects, tolerance and withdrawal. The technique used here allowed measurement of the changes in the same animal using spontaneous withdrawal rather than withdrawal precipitated by an opioid receptor

antagonist. Comparison between groups enabled demonstration of dose dependency for both direct effects and withdrawal.

The significant increase in systolic and diastolic blood pressure on the first day of opioid treatment is consistent with the transient increase in mean arterial blood pressure that were observed by other workers when morphine was administered (Gomes et al., 1976; Cruz and Villarreal, 1992). This result is also consistent with the generalised stimulant effect of morphine reported at low doses (Sloan et al., 1963; Fog, 1970; Yarbrough et al., 1971; Ayhan and Randrup, 1973). In these studies increases in grooming, motor activity, eating and drinking were observed at low morphine doses with a decrease in these activities at high doses. The locomotor data presented here demonstrate this dose dependent effect clearly. Morphine at 10 mg kg^{-1} day^{-1} caused a large increase in locomotor activity on days 1 and 2, 20 mg kg^{-1} day^{-1} caused a smaller response, and no stimulation was evident at 30 mg kg^{-1} day^{-1}.

The progressive dose dependent decrease in heart rate, systolic and diastolic blood pressure during morphine infusion observed here was not reported by other studies that employed a relatively higher concentration of morphine.

After the peak morphine depressive effect, systolic and diastolic blood pressures in our animals started to return to pre-morphine treatment levels, indicating the development of tolerance to the drug. This is consistent with those studies using behavioural responses to quantify tolerance produced by continuous infusion of morphine from osmotic pumps (Adams and Holtzman, 1990; Paronis and Holtzman, 1992). However, this effect was not apparent in the heart rate data and may indicate a differential development of tolerance for different opioid effects, as has been demonstrated by other workers (Brady and Lukas, 1984). A longer period of morphine treatment or a higher dose may have shown tolerance development to the heart rate effects of morphine.

During the phase of spontaneous withdrawal, systolic and diastolic blood pressure increased beyond pre-morphine levels for all doses of drug. These effects on blood pressure are similar to those reported by other workers (for mean arterial blood pressure) when morphine treatment is withdrawn (Buccafusco, 1983; Buccafusco et al., 1984; Marshall and Buccafusco, 1985). Heart rate only showed an increase over pre-morphine levels at a dose of 30 mg kg^{-1}. There was no increase in locomotor activity associated with the withdrawal phase. This is the first demonstration of a rebound increase in heart rate in an animal model of spontaneous opioid withdrawal. A rebound increase in heart rate is a characteristic withdrawal sign in humans (Kolb and Himmelsbach, 1938; Himmelsbach, 1942; Jasinski, 1977).

A number of differences between this study and other similar studies require comment. Although behavioural measures have been used for decades to assess opioid effects and withdrawal in animals, the limitations of these methods such as quantal measurement and reliance on experimenter observation have been recognised. The need for a more objective, sensitive indicator of opioid effects and withdrawal responses stimulated earlier studies which utilised cardiovascular changes as end points (Buccafusco, 1983). However, these studies were limited by the technology available at the time to assess cardiovascular parameters in experimental animals. Measurements of blood pressure were discontinuous (tail-cuff method) or required at least some limitation on the animals' normal movement (in-dwelling catheters) with the potential to cause stress (Buccafusco, 1983; Buccafusco et al., 1984; Marshall and Buccafusco, 1985). Any procedure, which is stressful and therefore increases endogenous opioid activity is likely to complicate the interpretation of experiments on opioid effects and should ideally be avoided. The use of miniaturised telemetry devices appears to address these limitations to a considerable extent (Irvine et al., 1997). Additionally, many studies have relied on withdrawal precipitated by opioid receptor antagonist administration. However, it is now known that opioid receptor antagonists produce a range of effects in non-dependent organisms, particularly if the baseline levels have been altered by stress. These include cardiovascular changes (Petty et al., 1996). In these experiments central administration of naloxone alone in morphine naive animals caused an increase in blood pressure. Hence, precipitated withdrawal induced changes may be confounding the direct effects of the antagonist with the changes resulting from withdrawal.

Previous studies have used daily doses of morphine, typically around 100 mg kg^{-1} day^{-1}, that are considerably higher than those used here, to induce dependence (Buccafusco, 1983; Marshall and Buccafusco, 1985). Our data demonstrate dose-related opioid withdrawal starting at much lower doses than those used previously. This improved sensitivity may be a consequence of the improved methodology for recording cardiovascular measures or of the sustained morphine delivery provided by the osmotic minipumps. The latter is less likely a reason for the improved sensitivity as other workers (Chang and Dixon, 1990) have used continuous delivery.

The vast majority of previous studies in this area have used precipitated withdrawal in their animal models (Marshall and Buccafusco, 1985; Buccafusco, 1990; Chang and Dixon, 1990). This method allows the withdrawal process to be over in a short period of time, which is convenient for the measurement of endpoints. It also probably increases the magnitude of the physiological responses compared to a spontaneous withdrawal situation and thus improves the sensitivity of the measurement technique. However, opioid withdrawal in humans is a process that takes hours or days and therefore, the spontaneous withdrawal model in animals is much more appropriate. It was pointed out that all signs of precipitated abstinence are not related linearly to the degree of depen-

dence (Bläsig et al., 1973) and not all these signs were equally sensitive to naloxone (Wei et al., 1973).

In this report, the tolerance and withdrawal effect of morphine on heart rate did not parallel the changes in systolic and diastolic blood pressure. It is apparent that all signs of tolerance and physical dependence do not evolve or become manifest in parallel. Even blood pressure and heart rate, both cardiovascular parameters, are still independent of each other. To date, we are still not clear which signs are related to symptoms that lead to continued drug seeking behaviour, relapse, and the exacerbation of psychopathy. Different signs and symptoms of abstinence have different neuronal substrates; thus, quantifying opioid tolerance, physical dependence and abstinence simultaneously is essential to the design of future studies to examine the neuronal bases for these phenomena.

The results obtained in the present study, by using a more sensitive method to measure cardiovascular signs, enable continuous measurement of spontaneous opioid withdrawal in freely moving rats. This model might therefore be useful in monitoring withdrawal-induced cardiovascular changes simultaneously with changes in locus coeruleus monoamine metabolism measured by microdialysis methods (Javelle et al., 1997). This would provide a more direct link between opioid-induced changes in locus coeruleus function and the expression of opioid withdrawal.

In conclusion, we have demonstrated that cardiovascular measures using telemetry can provide an objective and sensitive animal model of opioid effects and withdrawal in freely moving animals. The low doses of morphine required and the clear effects with non-precipitated withdrawal should provide a useful animal model for the study of opioid effects relevant to the human situation. In addition, the increased sensitivity of this model may be useful for understanding the mechanisms of blood pressure changes during opioid withdrawal and for testing agents which may potentially alleviate opioid withdrawal. A large number of drugs have the potential to alleviate the symptoms of withdrawal (Bhargava, 1994, 1995) and these may be able to assist in the detoxification of opioid users.

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