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Naloxone suppression and morphine enhancement of voluntary wheel-running activity in rats

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Abstract

This study examines the effects of the opioid receptor antagonist, naloxone, and the agonist, morphine, on voluntary wheel-running activity (WR) in rats. Male Sprague–Dawley rats were given 1-h access to a running wheel under non-deprived conditions. Naloxone injections (1.0, 0.5, or 0.25 mg/kg, ip), administered immediately before access to running wheels, dose-dependently suppressed WR. In another experiment, subjects were given 6-h access to running wheels under nondeprived conditions for 5 consecutive days. Morphine injections (2.0 mg/kg, sc) were found to increase WR after an initial suppression. These data demonstrate that naloxone inhibits WR, while morphine both suppresses and enhances WR depending on time and dose. These are in agreement with data on other behaviors that indicate that endogenous opioid systems play a major role in the mediation of motivational behaviors.

Keywords: Wheel running; Opioids; Naloxone; Morphine; Rat

1. Introduction

Endogenous opioids play a major role in motivational behaviors. Low doses of the opioid antagonist naloxone inhibit food (Cooper and Turkish, 1989; Giraudo et al., 1993; Levine et al., 1995; Margules et al., 1978), water (Reid et al., 1981), and alcohol intake (Reid and Hunter, 1984). Moreover, similar doses have been shown to block self-stimulation and the effects of drug-induced enhancement of self-stimulation (Marcus and Kornetsky, 1973). Opioid agonists enhance food (Reid et al., 1981; Sanger and McCarthy, 1980, 1981; Sills and Vaccarino, 1998) and alcohol intake (Reid and Hunter, 1984), and self-stimulation performance (Marcus and Kornetsky, 1973).

Locomotor behaviors are also suppressed by naloxone (DeRossett and Holtzman, 1982; Pert et al., 1979). Morphine has a biphasic effect on open-field behavior (Browne and Segal, 1980; Sanger and McCarthy, 1980)—an initial decrease followed by an increase. Wheel-running activity (WR) is also decreased by naloxone (Boer et al., 1990). Although open-field activity and WR are both motor behaviors with obvious similarities, they are actually different motivational behaviors. Correlations between simple measures of activity and wheel running are very low (Anderson, 1937; Eayrs, 1954; Finger, 1961). Rats that spontaneously run at high rates do not necessarily show high levels of activity in an open field. Conversely, rats that are highly active in an open field may not engage in high levels of WR.

Further evidence for the unique motivational aspects of WR is found when one compares the effects of drugs on these two behaviors. Administration of amphetamine results in increases in locomotor activity (LM), but decreases in WR (Della Maggiore and Ralph, 2000; Serwatkiewicz et al., 2000). However, drug effects seem to be a function of the amount of wheel experience (Vilaysinh and Eikelboom, 2000). Vilaysinh and Eikelboom (2000) demonstrated that 3.0 mg/kg amphetamine results in an elevation of WR in animals with 24 days of continuous wheel access. These disparate effects are not specific to pharmacological manipulations. In rats, hippocampal and medial septal lesions increase exploration in an open field, but decrease WR in the home cage (Grossman,

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1977; Whishaw and Jarrad, 1995). Although the low correlation between these two motor behaviors was demonstrated several decades ago (Anderson, 1937; Eayrs, 1954), the two behaviors are still sometimes used interchangeably as measures of activity (Schnur, 1985; Schnur and Barela, 1984; Schnur et al., 1983a,b).

Wheel running and locomotor behavior have distinct motivational features. WR shows a complex interaction with feeding behavior. Rats deprived of food run significantly more than nondeprived controls (Finger, 1951), and rats deprived of food for 72 h run more than those deprived only for 24 h (Finger, 1951). Likewise, rats given alternate-day access to running wheels show reduced food consumption on "wheel days" in comparison to non-wheel days (Mueller et al., 1997). In the most striking demonstration of this interaction, rats housed in activity wheels with limited food access will run to the point of starvation and death (Routenberg and Kuznesof, 1967; Spear and Hill, 1962). Food deprivation is less reliable in increasing open-field activity and other measures of "generalized activity" than it is in increasing WR (Campbell et al., 1961; Treichler and Hall, 1962; Weasner et al., 1960).

The endogenous opioids are important in the regulation of feeding behavior. Morphine produces increases in food intake (FI), usually following an initial period of food-intake suppression, in both food-deprived and freely feeding animals (Gosnell and Krahn, 1993; Sanger and McCarthy, 1980, 1981; Sills and Vaccarino, 1998). These increases are dependent on time and dose, as well as the food deprivation condition. Conversely, naloxone reliably suppresses FI in both food-deprived and freely feeding animals (Margules et al., 1978; Reid et al., 1981). Furthermore, selective mu and kappa receptors antagonists decrease spontaneous nocturnal and deprivation-induced feeding (Arjune et al., 1990; Bakshi and Kelley, 1993; Gulati et al., 1991; Levine and Billington, 1989; Ukai and Holtzman, 1988).

In this study, it was hypothesized that endogenous opioids would affect wheel-running behavior similarly to its effects on feeding and drinking behavior. That is, we expected the opioid antagonist, naloxone, to suppress WR, and the opioid agonist, morphine, to enhance it, following an initial suppression. Previous wheel-running studies (Boer et al., 1990; Carey et al., 1981) have measured WR using apparatus that limit activities outside the running wheel (e.g., conventional Wahmann activity wheels with suspended metal cages). Conventional side cages do not provide ample space for ambulating and grooming behaviors. Pilot data in our laboratory demonstrated that the size of the side cage effects amount of WR. That is, rats in wheels with smaller side cages run more than rats placed in wheels with larger side cages. It appears that small cages may be a stimulus that elicits increased time spent in the running wheel, and, hence, increased running activity. By using larger side cages, this potential confounding variable was controlled. Other investigators (Boer et al., 1990) have restricted food access to induce high running rates. Although higher running rates are observed, rats are food-deprived adding another potential confounding variable. Because the goal of the present study was to measure *voluntary* WR, no aversive conditions, either food deprivation or restricted mobility, were used to induce running. Food and water were available ad libitum. Conventional Wahmann activity wheel side-cages were replaced with larger cages in order to provide animals with ample space to engage in a variety of behaviors other than running, such as grooming, ambulation, feeding, and drinking.

2. Experiment 1

2.1. Methods

2.1.1. Subjects

Sixteen male Sprague–Dawley albino rats weighing 425–550 g at the start of the experiment were used as subjects (Charles River Laboratories, Wilmington, MA). They were housed in a vivarium held at 22° ± 2 °C and maintained at 30–40% humidity. All rats were kept on a 12:12-h reverse light–dark cycle. Home cages were plastic cages (20.3 cm^3). All rats had food and water ad libitum throughout the duration of the experiment.

2.1.2. Apparatus

Eight Wahmann (Baltimore, MD) activity wheels, 33 cm in diameter, were used. A shoebox cage (27.9 × 30.5 × 12.6 cm) was attached to the wheel with a window (8.9 × 7.6 cm) that allowed access to the wheel. A magnetic switch (Happ Controls, Elk Grove, IL) was attached to the back of the wheel and a magnetic rod was attached to the wheel's axle. Magnetic switch closures were recorded as revolutions.

2.1.3. Procedures

Subjects were run in two groups of eight. Light cycles were arranged so that both groups were placed in running wheel cages during the 3rd hour of their dark cycle. In pilot studies, this was found to be a period of high activity. Lights were off between 07:00 and 19:00 h with daily testing beginning at 10:00 for Group 1. Lights were off between 12:00 and 24:00 h with daily testing beginning at 15:00 for Group 2. Animals were given access to the wheels for 1 h. Once running activity had reached asymptote for both groups, 3 days of vehicle injections, 1 ml/kg, were administered into the intraperitoneal (ip) cavity. Following this baseline period, vehicle was administered for one session immediately before (pre-drug) and one session immediately following (post-drug) naloxone injection. Animals were given injections immediately before being placed in the wheel running apparatus. Each animal received all doses of naloxone (1.0, 0.5, or 0.25 mg/kg, ip) in descending order. A minimum of 3 days was allowed between doses. This experimental protocol was approved by an Institutional Animal Care and Use Committee.

2.1.4. Drugs and injections

Naloxone HCl (Research Biochemicals, Natick, MA) was prepared in 1 mg/ml in 0.9% saline.

2.1.5. Data analysis

Wheel-running data were analyzed in total revolutions per hour. Throughout the experiment, data analysis was carried out with planned comparisons of specific contrasts using Student's *t* test. Naloxone suppression was computed as the difference between pre-drug revolutions and revolutions on the day of naloxone injections. Baseline was calculated as the mean of the 5 days of activity prior to the first pre-drug condition.

2.2. Results

Running activity had reached asymptote in both groups by the 17th session. Because mean revolutions were not significantly different between groups [$t(15) = 0.42$, $P > .05$], data were combined for analyses ($N = 16$). Naloxone produced dose-dependent suppression of WR (see Fig. 1). Mean revolutions after administration of 1.0 mg/kg naloxone were significantly less than in the predrug condition [$t(15) = 5.80$, $P < .05$]. This demonstrated a reduction of 62.7%. Mean revolutions after 0.5 mg/kg naloxone were also significantly less than in the predrug condition [$t(15) = 4.81$, $P < .05$]. This demonstrated a reduction of 50.6%. Mean revolutions after 0.25 mg/kg naloxone were significantly less than the predrug condition, 105.1 [$t(15) = 3.08$, $P < .05$]. This demonstrated a 25.5% reduction.

2.3. Discussion

The opioid receptor antagonist, naloxone, dose-dependently suppressed WR. These data are in agreement with other data by Boer et al. (1990). However, there are two important differences between Boer et al.'s study and this one. Boer et al.'s lab used a very high dose of naloxone (50 mg/kg), as well as food deprived rats to induce high running rates. Carey et al. (1981) found that naloxone failed to suppress WR. These differences in our data may be due to differences in experimental design. In the present experiment, the first hour immediately following naloxone administration was evaluated, whereas in Carey et al. (1981), revolutions were accumulated over a 3-h period following naloxone administration. Thus, naloxone's ability to suppress WR is probably short-term and may be masked when longer periods of activity are analyzed. Furthermore, baseline activity levels in their study was quite low (25% of the baseline activity exhibited by our subjects), which makes the lack of naloxone suppression difficult to interpret. It is also important to note that at similar doses to the ones used in this study (0.5 and 1.0 mg/kg), spontaneous motor activity is not suppressed (Pert et al., 1979). This further demonstrates the differential effects of drugs on voluntary WR in comparison to locomotor behavior.

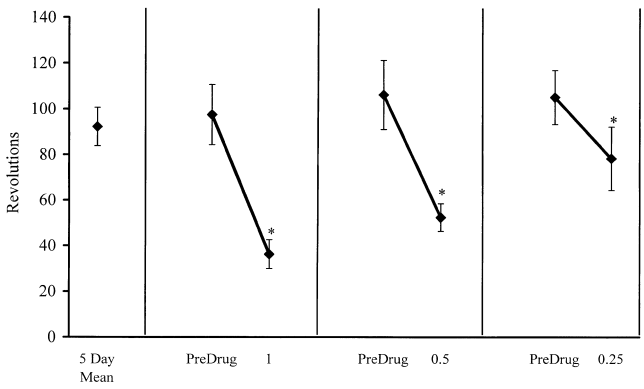

Fig. 1. Mean (±S.E.M.) WR over 1-h sessions after vehicle (predrug day) and naloxone (1.0, 0.5, and 0.25 mg/kg). 5-day baseline are the mean revolutions on the days immediately prior to the first predrug day and asterisks indicate significant differences (*t* test) from predrug WR.

The opioid antagonists naloxone or naltrexone do not suppress baseline running activity in mice (Brunello et al., 1984; Ukai and Kameyana, 1985) and male and female hamsters (Schnur and Barela, 1984). However, these antagonists do block morphine-induced increase in these species (Calcagnetti et al., 1987; Schnur and Ragioza, 1986). Thus, naloxone has a variety of effects that are dependent on species, although methodological differences in these studies make comparisons with the present study difficult.

3. Experiment 2

To further explore the role of endogenous opioid systems in WR, the effects of the opioid agonist morphine were examined. Based on the findings of the previous experiment that naloxone suppressed WR, morphine was expected to enhance WR. Similar to feeding studies (Sanger and McCarthy, 1981), this effect was expected to be biphasic and the stimulatory effects on WR were expected to occur 2 h after drug administration.

3.1. Methods

3.1.1. Subjects, apparatus, and injections

Animals from Group 2 in Experiment 1 were used in this experiment. At the start of this experiment, animals weighed 535–680 g. Housing and testing conditions remained the same as in Experiment 1. Morphine sulfate (Sigma, St. Louis, MO) was prepared in saline in 1 mg/ml. It was administered in ml/kg.

3.1.2. Procedures

Experiment 2 began 1 week after naloxone injections had been completed. Daily 1-h wheel access was continued. Three doses of morphine (1.0, 0.5, or 0.25 mg/kg) were administered to all animals subcutaneously (sc) in the

following order: 0.5, 1.0, and 0.25 mg/kg. Animals were given injections 90 min before being placed in wheel running apparatus. A minimum of 3 days was allowed between doses. Data were analyzed as in Experiment 1.

3.2. Results

The first dose of morphine, 0.5 mg/kg, abolished WR. Mean revolutions were significantly less than the predrug condition [$t(7) = 5.71$, $P < .05$]. However, the second dose of morphine, 1.0 mg/kg, yielded a significant increase in mean revolutions [$t(7) = 4.66$, $P < .05$]. At the lowest dose, 0.25 mg/kg, WR showed a nonsignificant decrease from the predrug condition [$t(7) = 0.80$, $P > .05$].

3.3. Discussion

Morphine completely suppressed WR at the 0.5 mg/kg dose. However, at the 1.0 mg/kg dose, there was a slight increase in WR. It is possible that there is a change in morphine effects with repeated experience. Initially, morphine has a suppression effect. After repeated injections, it has a stimulatory effect. This is consistent with the pattern of tolerance often seen with morphine. The effects at the 0.25 mg/kg dose showed no difference in WR. This dose may have been too small to detect changes in WR.

Morphine has a complex profile. It has strong sedative effects coupled with delayed stimulant actions (Domino et al., 1976) that are dependent on time, dose, species, strain, age, and weight. The effects of morphine are highly variable with FI; increases occurring as early as 1 h and as late as 6 h after injections (Sanger and McCarthy, 1980) have been observed. Given its complexity, it can be difficult to detect morphine's delayed stimulant actions on wheel running behavior. Thus, a third experiment was designed that gave greater consideration to the varying effects of morphine over time.

4. Experiment 3

Based on the results of the previous experiment, the third experiment was undertaken to better determine the time course of morphine's effects. Although 1-h wheel access was sufficient to measure the effect of naloxone, the effects of morphine are less immediate and continue up to 6 h after a single injection. Increases in FI have been observed between 1 and 6 h postinjection (Sanger and McCarthy, 1980). In the present experiment, rats were given 6-h wheel access immediately after receiving morphine injections.

4.1. Methods

4.1.1. Subjects, apparatus, and injections

The same rats from Experiment 2 served as subjects in the present experiment. Subjects weighed 615–845 g at the start of the experiment. Housing conditions remained the same as in the previous two experiments. Morphine sulfate was prepared in saline and administered subcutaneously. It was prepared in 1 mg/ml and administered in mg/kg.

4.1.2. Procedures

Animals were given 6-h access to running wheels. Animals were placed in wheels at the onset of their dark cycle. Activity stabilized after 3 days. Saline vehicle was administered on the 4th and 6th days of baseline. On the 7th day, morphine (2.0 mg/kg, sc) was administered and rats were immediately placed in the running wheel apparatus for 6 h. Mean total revolutions were calculated for each hour of wheel access, a total of 6 h. Morphine conditions were compared to pre-drug activity. Data analysis was carried out with planned comparisons of specific contrasts based upon a two-way, repeated-measures ANOVA (2 (Drug) × 6 (Time)). Planned contrasts and significant main and interaction effects were subsequently explored using Student's *t*.

4.2. Results

The two-factor ANOVA yielded significant main effects for drug [$F(1,84) = 3.87$, $P = .05$], Time [$F(5,84) = 4.12$, $P < .05$], and Drug × Time [$F(5,84) = 2.39$, $P < .05$] for the 2.0 mg/kg dose of morphine. As expected, there was an initial suppression of WR during the 1st hour of activity. However, there was a significant increase in the 2nd hour [$t(7) = 3.62$, $P < .05$], 3rd hour [$t(7) = 2.34$, $P < .05$], and 5th hour [$t(7) = 2.75$, $P < .05$] of activity compared to predrug (see Fig. 2). Activity returned to predrug levels during the 6th hour.

4.3. Discussion

Because feeding and wheel running behavior interact (Finger, 1951; Looy and Eikelboom, 1998; Spear and Hill,

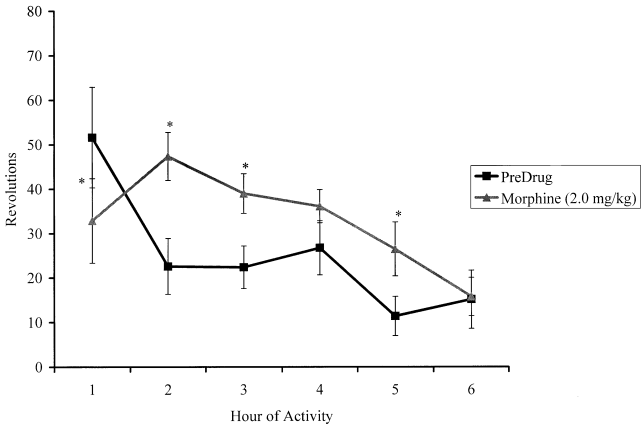

Fig. 2. Mean (±S.E.M.) WR over 6-h access after vehicle (predrug day) and morphine (2.0 mg/kg). Asterisks indicate significant differences (*t* test) from predrug WR.

1962), it was expected that morphine would have similar effects on WR as has been observed with FI. Morphine indeed produced a biphasic effect on WR similar to that observed with FI. There was an initial suppression of activity, followed by an increase in activity. This is in agreement with feeding studies demonstrating that morphine's biphasic effect is dependent on both time and dose. It has been demonstrated (Sanger and McCarthy, 1980) that 1.0 and 3.0 mg/kg morphine increase FI at 2 h post-injection, while 10 mg/kg induced a sharp increase at 4 h that continued to rise at 6 h post-injection. These data are also in agreement with locomotor studies demonstrating the biphasic effect of opioid agonists (Browne and Segal, 1980).

In the present study, at 2.0 mg/kg, a biphasic effect was observed; the initial suppression was followed by a 110% increase of WR during the 2nd hour, a 74% increase during the 3rd hour, and a 132% increase during the 5th hour. A non-significant increase was observed during the 4th hour followed by a return to baseline during the 6th hour. These data are consistent with the suppression and enhancement effects of morphine on motivational behaviors.

Because the same subjects were used throughout this series of experiments, the animals were quite large by the time of the third experiment. As a result of their age and size, their baseline running activity decreased from the first experiment by approximately 50 revolutions. In addition to age and body weight, strain is also an important factor that affects the amount of baseline running. The Sprague–Dawley rat strain is one of the lowest strains of spontaneous runners while Spontaneous Hypertensive Rats (SHR) and Wistar show much higher baseline levels (Shyu et al., 1984). Male subjects were also used which emit lower rates than females. Although the subjects used in these experiments showed relatively low running rates, the opioid agonist effects on WR are consistent with patterns observed in hamsters (Schnur, 1985; Schnur and Barela, 1984; Schnur et al., 1983a) and mice (Browne and Segal, 1980; Ukai and Kameyana, 1985) and were robust enough to show both significant increases and decreases after morphine administration. This research demonstrates the importance of opioid systems in both low and high running strains.

5. General discussion

These data demonstrate that the naloxone-induced suppression and morphine-induced enhancement effects on feeding and LM can be extended to include WR. This effect has previously been demonstrated in hamsters (Schnur and Barela, 1984; Schnur et al., 1983b) and in mice (Calcagnetti et al., 1987).

Moreover, the correlation of simple measures of LM with WR is quite low (r=.18) (Eayrs, 1954). In a prior research, Lewis (unpublished) found that amphetamine increased open-field activity, but had no effect on WR. More recently, this effect was replicated in other laboratories (Della Maggiore and Ralph, 2000; Serwatkiewicz et al., 2000). Conversely, estradiol increases WR, but not LM (Fahrbach et al., 1985). Vilaysinh and Eikelboom (2000) found a similar suppression effect in wheel-naive rats; however, in rats that had ad lib wheel access for 24 days, there was an enhanced effect on WR.

Although the correlation between WR and LM is low, opioid receptor agonists enhance both forms of motor behavior. For instance, intracerebral (Stinus et al., 1980; Vaccarino et al., 1986), intraventricular (Pert et al., 1979), and systemic (Pert et al., 1979; Swerdlow et al., 1985) injections of opioid agonists all increase LM. Furthermore, several investigators reported a biphasic effect on LM—initial suppression followed by enhancement of activity. Although the time course is often shorter, occurring over a 3-h period, a biphasic effect over 6 h has been reported in LM (Pert et al., 1979).

Several investigators have reported similar effects of morphine on WR in hamsters (Schnur and Ragioza, 1986; Schnur et al., 1983b) and mice (Brunello et al., 1984), although opioid antagonists alone apparently do not affect baseline running activity in these species. This study demonstrates that low doses of naloxone dose-dependently suppress spontaneous WR in the Sprague–Dawley rat.

In the present study, Sprague–Dawley rats were chosen because of the extensive research on both behavior and neuropharmacology of the line despite their relatively low level of running behavior. Although the rats used in the present study were larger and older than those typically used in behavioral and pharmacological research, the results with naloxone are in agreement with data on younger and lighter animals (Boer et al., 1990). Moreover, the WR was sufficient to show both naloxone-induced suppression and morphine-induced suppression and increases in WR.

Because the same subjects were used throughout this study, by the third experiment, animals had experience with repeated administration of opioid receptor agonists and antagonists. While it is well established that tolerance and sensitization occur as a result of repeated exposure to morphine, the doses used in such paradigms are much higher than the ones used in the present study and are also administered chronically (Cox, 1993). In this study, the largest dose given was 2.0 mg/kg, and this was the final dose administered. All other doses were 1.0 mg/kg or smaller. In addition, several days of no injections were scheduled before a second injection was ever given. While changes in receptor regulation were not directly measured, an acute, low-dosage regimen was used to minimize such alterations. One cannot rule out the possibility of some sensitization or tolerance developed at these doses; however, they are not likely to account for the major effects on WR observed in this experimentation.

Endogenous opioids also have been demonstrated to play a role in running and other forms of exercise. Short-term moderate exercise in nondeprived Sprague–Dawley rats results in increased supraoptic hypothalamic dynorphin-A

content (Aravich et al., 1993). Plasma beta-endorphin levels increase after exercise in both animals and humans (Appenzeller et al., 1980; Carr et al., 1981; Colt et al., 1981; Sforzo et al., 1986). Chronic running behavior reduces the density of opioid receptors; this finding may be a result of higher levels of endogenous opioids, which downregulate receptors (Houghten et al., 1986). Mice exhibit classic opiate withdrawal symptoms after chronic swim stress (Christie and Chesher, 1982). The limitation of some of these studies (Christie and Chesher, 1982; Houghten et al., 1986) is that exercise was not voluntary, but was forced using treadmills paired with shock or swim-stress.

One of the implicit goals of this research was to test the usefulness of a voluntary model of running. No aversive consequences or food deprivation were employed to motivate WR. Animals had ample cage space and free choice to engage in a variety of behaviors, including feeding, drinking, grooming, and exploring. The wheel apparatus was specially designed to provide such choices. Stable activity rates were achieved by allowing daily, 1-h wheel access. The use of this experimental paradigm may provide the opportunity to better understand the neurobiological basis of the motivation for activity and its interaction with other motivational systems.

The neurobiology underlying wheel-running behavior is relatively unexplored in comparison to other motivational behaviors, such as feeding, drinking, and drug reinforcement. As with these, WR has been shown to function as a reinforcer (Iverson, 1993). Moreover, rats and other rodents spontaneously emit high rates of WR under ad libitum food and water conditions. The present data suggest an important role for endogenous opioid systems in this behavior and may model similar neurochemical functions in aerobic exercise and the motivation to engage in these behaviors.

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