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Behavioral characterization of morphine effects on motor activity in mice

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Abstract

A biphasic effect of morphine on locomotion has been extensively described. Nevertheless, the effects of this opioid on other behavioral parameters have been overlooked. The aim of the present study was to verify the effects of different doses of morphine on motor behaviors observed in an open-field. Adult female mice were injected with saline or morphine (10, 15 and 20 mg/kg, i.p.) and observed in an open-field for quantification of locomotor and rearing frequencies as well as duration of immobility and grooming. The lowest dose of morphine decreased locomotion (and increased immobility duration) while the highest dose increased it. All doses tested decreased rearing and grooming. Thus, the effects of morphine on locomotion do not parallel to its effects on rearing and grooming. Our results indicate that locomotion not always reflects the effect of drugs on motor activity, which can be better investigated when other behavioral parameters are concomitantly taken into account.

Keywords: Morphine; Motor behavior; Open-field; Mice

1. Introduction

Several studies have focused on the locomotor effects of morphine. In this respect, a stimulant as well as a depressive locomotor effect of this opioid has been reported depending on the dose and the interval after administration (Herman et al., 1979; Székely et al., 1980; Longoni et al., 1987; Narita et al., 1993; Funada et al., 1994; Belknap et al., 1998; Dogrul et al., 1999; Manzanedo et al., 1999; Rodrigues-Arias et al., 2000).

While mesolimbic dopaminergic system has been related to the hyperlocomotion induced by several psychostimulants (Kelly et al., 1975; Kelly and Iversen, 1976; Swerdlow and Koob, 1985; Vaccarino et al., 1986), the participation of this pathway in opioid-induced hyperlocomotion has been ruled out (Kalivas et al., 1983; Amalric and Koob, 1985; Vaccarino et al., 1986; Murphy et al., 2001). Thus, the effects of morphine on locomotor behavior seems to be complex from a neurochemical point of view. From a behavioral perspective, locomotion can be modified by the concomitant expression of other motor behaviors (Bernardi et al., 1986; Chinen et al., in press). Nevertheless, the effects of morphine on motor behaviors other than locomotion have received much less attention. Within this context, the concomitant analysis of several motor behaviors would be enriching and could provide more accurate information about the motor function alterations following morphine administration. In this way, the open-field paradigm has been extensively used to study motor as well as exploratory behaviors (Frussa-Filho and Palermo-Neto, 1988, 1991; Silva et al., 1996; Abílio et al., 1999, 2003; Prut and Belzung, 2003; Araujo et al., 2004; Frussa-Filho et al., 2004). The aim of the present work was to investigate the effects of different doses of morphine on several motor behaviors observed simultaneously in an open-field.

2. Material and methods

2.1. Subjects

Healthy adult (3 months of age) female EPM-1 mice, born and raised under our laboratory conditions, were

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used. Female mice were used on the basis of the greater locomotor stimulation induced by morphine in this gender (Holtman et al., 2004). The animals were housed under conditions of controlled temperature (22–23 °C) and under a 12 h light/dark cycle with lights on at 7:00 am. Food and water were available ad libitum throughout the experiment. Animals used in this study were maintained in accordance with the guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council, USA.

2.2. Drugs

Morphine sulfate (Sigma Chemical Co., St. Louis, MO) was diluted in saline. Saline was used as vehicle. Morphine and its vehicle were administered intraperitoneally *in a volume of 10 ml/kg body weight.*

2.3. Procedure

Animals were injected with saline or 10, 15 or 20 mg/kg morphine ($n=10$). Thirty minutes later, mice were placed individually in the center of an open field arena — a circular box (40 cm in diameter and 50 cm high) with an open-top and a floor divided into 19 squares. Locomotion (number of floor units entered) and rearing (number of times the animal stood on hind legs) frequencies as well as immobility duration (total seconds of lack of movements) and grooming (total seconds of mouth or paws on the body and on the head) duration were simultaneously measured during 5 min.

2.4. Statistical analysis

Data were analyzed by one-way analysis of variance (ANOVA) followed by Duncan's test. To verify a possible correlation among open-field behaviors, Pearson's correlation test was applied. A probability of $p<0.05$ was considered to show significant differences for all comparisons made.

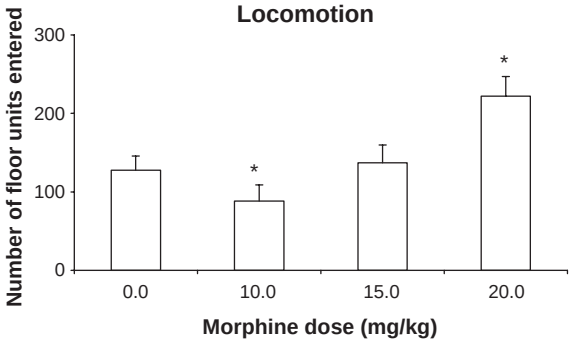

Fig. 1. Effects of morphine administration on open-field locomotor behavior of mice. Data are expressed as *mean ± S.E.M*. Analysis of variance followed by Duncan's test. *$P<0.05$ when compared to all the other groups.

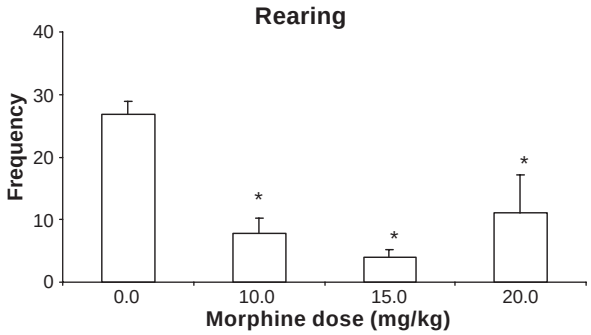

Fig. 2. Effects of morphine administration on open-field rearing behavior of mice. Data are expressed as *mean ± S.E.M*. Analysis of variance followed by Duncan's test. *$P<0.05$ when compared to saline-treated group.

3. Results

The lowest dose of morphine decreased locomotion frequency while the highest dose increased it (Fig. 1). Thus, mice treated with 10 and 20 mg/kg morphine presented a decrease and an increase in locomotion, respectively, when compared to saline-treated animals [F (3,36)=11.52, $p<0.0001$]. Mice treated with 15 mg/kg morphine did not present any difference in locomotion when compared to saline-treated animals, but presented an increase and a decrease in locomotion when compared to 10 and 20 mg/kg morphine-treated mice, respectively.

All doses of morphine decreased rearing (Fig. 2). Thus, mice treated with 10, 15 or 20 mg/kg morphine presented a decrease in rearing frequency when compared to saline-treated animals [F (3,36)=7.31, $p<0.001$]. There were no differences among morphine-treated groups.

Morphine at the dose of 10 mg/kg increased immobility (Fig. 3). Thus, 10 mg/kg morphine-treated mice presented an increase in duration of immobility when compared to all the other groups [F (3,36)=5.14, $p<0.005$]. Mice treated with 15 or 20 mg/kg morphine did not present any

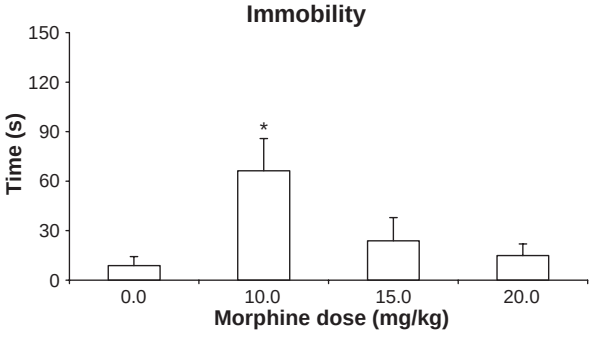

Fig. 3. Effects of morphine administration on open-field duration of immobility of mice. Data are expressed as *mean ± S.E.M*. Analysis of variance followed by Duncan's test. *$P<0.05$ when compared to all the other groups.

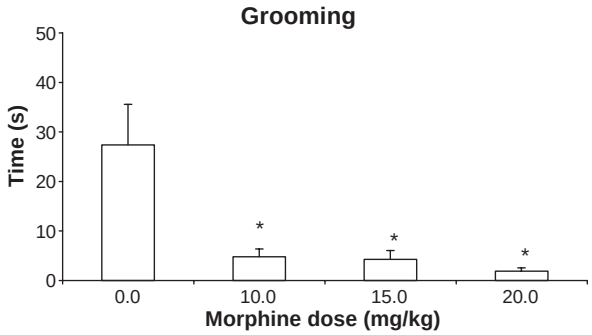

Fig. 4. Effects of morphine administration on open-field grooming behavior of mice. Data are expressed as *mean* ± *S.E.M*. Analysis of variance followed by Duncan's test. *$P<0.05$ when compared to saline-treated group.

difference in duration of immobility when compared to saline-treated animals, but presented a decrease in duration of immobility when compared to 10 mg/kg morphine-treated mice.

All doses of morphine decreased grooming (Fig. 4). Thus, mice treated with 10, 15 or 20 mg/kg morphine presented a decrease in grooming duration when compared to saline-treated animals [F (3,36)=14.59, $p<0.0001$]. There were no differences among morphine-treated groups.

Pearson's correlation test revealed a positive correlation between rearing and grooming behaviors as well as a negative correlation between duration of immobility and locomotion and duration of immobility and rearing behavior (Table 1).

4. Discussion

Our results show that the lowest dose of morphine decreased locomotion (and increased duration of immobility) while the highest dose increased it. In addition, rearing frequency as well as grooming duration were decreased by all doses of morphine.

As commented earlier, morphine effects on locomotor activity depend on the dose used. Thus, in mice a range of doses from 3 to 10 mg/kg elicited an initial depression followed by hyperlocomotion (Székely et al., 1980). On the other hand, other authors have found only hyperlocomotion with doses between 10 and 40 mg/kg (Herman et al., 1979; Longoni et al., 1987; Narita et al., 1993; Funada et al., 1994; Dogrul et al., 1999; Manzanedo et al., 1999). In addition, Rodriguez-Arias et al. (2000) describe an increase in the locomotion frequency of mice treated with 25 and 50 mg/kg but no changes with lower doses. Finally, using 15 different mouse strains, Belknap et al. (1998) describe a depressive and a stimulant effect of respectively lower and higher doses of morphine (4 – 32 mg/kg) in the majority of them. In this respect, our data also show a biphasic effect of morphine on the locomotor behavior of mice with a depressor effect with 10 mg/kg and a stimulant effects with 20 mg/kg.

One could hypothesize that the locomotor effects of morphine would influence the manifestation of other motor behaviors due to behavioral competition. This does not seem to be the case since all doses of morphine decreased rearing frequency and duration of grooming. In addition, no correlation was observed between locomotion and rearing or grooming behaviors. Reinforcing the absence of behavioral competition, a much lower dose of morphine (0.5 mg/kg) increased both locomotion and rearing observed in rats (Lecca et al., 2004). The present results indicate that morphine differentially alters the neuroanatomical substrates specifically related to these behaviors.

Regarding the effects of morphine on locomotion, an injection of this drug either in the ventral tegmental area or in the nucleus accumbens produces, depending on the dose used, hyperlocomotion or an initial inhibition of activity followed by desinhibition (Cunningham and Kelly, 1992; Bauco et al., 1993). In addition, morphine at the same doses that induce hyperlocomotion also induces an increase in the release of mesolimbic dopamine (Di Chiara and Imperato, 1988a,b; Di Chiara, 1995; Pontieri et al., 1995; Bassareo et al., 1996). On the other hand, mesolimbic dopaminergic pathway does not seem essential to the hyperlocomotion induced by opiates. Indeed, pharmacological blockade of dopamine receptors or 6-hydroxy-dopamine destruction of dopamine terminals within the nucleus accumbens does not inhibit the locomotor activating property of systemically administered heroin (Vaccarino et al., 1986). In addition, heroin-stimulated locomotion is antagonized by blockade of opioid receptors within the nucleus accumbens (Amalric and Koob, 1985). Finally, the administration of an enkephalin analog into the nucleus accumbens induces locomotor activation, which is not attenuated by destruction of the mesolimbic dopamine system (Kalivas et al., 1983). It is important to note that the above-mentioned evidences were obtained in rats and caution should be taken when considering these evidences to discuss our behavioral data obtained in mice. However, a dopamine-independent mechanism related to morphine-induced hyperlocomotion has been also demonstrated in mice. Indeed, Murphy et al. (2001) have showed that there are no correlations between

Table 1
Correlation coefficients (Pearson's test) among the open-field behaviors

	Locomotion	Rearing	Grooming	Immobility
Locomotion		0.1947 $p=0.229$	−0.1317 $p=0.418$	−0.6442 $p=0000$
Rearing	0.1947 $p=0.229$		0.4017 $p=0.010$	−0.3999 $p=0.011$
Grooming	−0.1317 $p=0.418$	0.4017 $p=0.010$		−0.1843 $p=0.255$
Immobility	−0.6442 $p=0.000$	−0.39999 $p=0.011$	−0.1843 $p=0.255$	

morphine-induced locomotion and mesolimbic dopamine release in several strains of mice.

Considering rearing frequency, a decrease was induced by all the doses of morphine used. In this respect, although there are data showing that opioid peptides cause increases in rearing frequencies (Meyer et al., 1995; Bujdosó et al., 2001a,b) and the opioid antagonist naltrexone can reduce rearing activity (Rotta et al., 1988; Rocha and de Mello, 1994; Balcells-Olivero and Vezina, 1997), our results are in accordance with the study of Kuzmin et al. (2000) which demonstrated that 20 mg/kg morphine produced a decrease in rearing frequency of mice, concomitantly to a tendency towards an increase in locomotion frequency. In the same way, 30 mg/kg morphine produced an increase in locomotion and a decrease in rearing frequency (Laviola et al., 1994). In addition, increased rearing is one of the typical withdrawal symptoms after cessation of chronic administration of opiates (Hoshi et al., 2000; Nakagawa et al., 2000; Rockhold et al., 2000; Samini et al., 2000; Tokuyama et al., 2000; Tsuji et al., 2000). It should be considered that different pharmacological profiles of the drugs used in these studies could explain the different results described.

Similarly to rearing results, grooming behavior was also decreased by all the doses of morphine, and a positive correlation between rearing and grooming behaviors was observed. In this respect, Laviola et al. (1994) describe a decrease in grooming concomitant to an increase in locomotion in mice treated with 30 mg/kg morphine. It is interesting to note that rearing behavior is related to exploratory activity (Rotta et al., 1988; Crusio, 2001) and grooming behavior can be modified as a consequence of stress (Ducottet and Belzung, 2004). In this way, morphine presents aversive properties and produces controversial effects on anxiety levels (Anseloni et al., 1999*;* Patti et al., submitted). Thus, one should consider that the effects of morphine on emotional aspects could account for the different results found for locomotion, rearing and grooming behaviors.

In conclusion, our data show that morphine differentially modifies motor behaviors: the well-documented biphasic effect of morphine seems to be specifically for locomotor activity. Interestingly, concerning motor activity as a whole an inhibitory effect was verified since the duration of immobility was increased by the lowest dose (10 mg/kg) of morphine only. In this respect, duration of immobility negatively correlated to locomotion as well as to rearing frequencies. These results indicate that locomotion not always reflects the effect of drugs on motor activity, which can be better investigated when other behavioral parameters are concomitantly taken into account.

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