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Research Report

Irregular morphine administration affects the retention but not acquisition of conditioned place preference in rats

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ABSTRACT

Drug addiction is increasingly viewed as the expression of abnormal associative learning following repeated exposures to the drugs of abuse. Previous studies have demonstrated that the patterns of repetition such as frequency and spacing are important to many kinds of learning and memory retention. We hypothesized that drug repetition pattern might affect the reward-related learning although the total doses of the drug were the same. In the present study, we tested morphine-induced place preference following either regular or irregular pattern of morphine pairing in rats. Regular morphine group received morphine administration daily at a regular time with the same dose. Irregular morphine groups received morphine administration either at the same time but irregular doses, irregular time but same dose, or irregular time and irregular doses. We found that rats, who received irregular morphine pairing, exhibited similar acquisition of place preference but different preference retentions compared with regular morphine-treated rats after the same total dose of morphine. Rats, who received morphine administration at the same time but irregular doses and at irregular time and irregular doses, showed rapid disruption of place preference than the regular morphine group. Rats, who received morphine at irregular time but the same dose, showed similar retention of place preference to regular morphine group. Our results suggest that the pattern of drug pairing plays an important role in the retention of reward-related memory. This study may provide new evidence to broaden our understanding of the development and maintenance of drug craving.

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1. Introduction

Conditioned place preference (CPP) paradigm has been proposed as an animal model for testing the reward related learning and drug craving (Tzschentke, 2007). CPP measures the learning process and provides unique information about the rewarding effect of contextual cues associated with a drug stimulus during drug craving and seeking in drug

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cessation period (Bardo and Bevins, 2000). In the place preference conditioning paradigm, the unconditioned stimulus (US, reward) is repeatedly paired with conditioned stimuli (CS, environment cues) which acquire the motivational properties of the unconditioned stimulus (Pavlov 1927; Hoffman 1989).

This kind of reward-related learning can be influenced by a variety of experimental factors (Bardo et al., 1995; van Ree et al., 1999), such as dose of drug, the number of drug–context pairings (Brabant et al., 2005), conditioning trial duration, injection time and temporal relation between US and CS (Cunningham et al., 1999), the interval between drug injection and onset of conditioning (Ettenberg et al., 1999; Pliakas et al., 2001), conditioning and testing during day or night (Kurtuncu et al., 2004). However, all of these studies used regular and standard conditioning procedures, i.e., one or two conditioning sessions per day by alternating the drug and vehicle; fixed dose of drug in each conditioning; drug administration followed immediately conditioning session (Tzschentke, 2007). It is little known whether CPP will be influenced if these regular and standard procedures are disrupted.

It is widely accepted that repeated pairings of two independent stimuli are necessary for forming a firm associative memory. The pattern of repetition (such as frequency and spacing) plays a crucial role during many kinds of learning and memories (Cepeda et al., 2006; Donovan and Radosevich 1999; Janiszewski et al., 2003). CPP is also a kind of memory which is based on repeated pairings of a reward and a specific environment. We previously demonstrated that somatic sensory information is necessary for the acquisition of the reward-related learning (Meng et al. 2009). However, the role of drug pairing pattern in this drug-related memory process is still unknown. Here, we investigated whether the pattern of drug administration (regular or irregular) could affect the acquisition and/or the retention of conditioned place preference. During the conditioning session, regular morphine pairing group received morphine administration at a regular time with a fixed dose. On the other hand, irregular morphine groups received morphine administration either at the same time but irregular doses, irregular time but fixed dose, or irregular time and irregular doses. To our knowledge, this has not been studied yet. The present results demonstrated that irregular morphine repetition pattern can affect the retention but not the acquisition of morphine-induced conditioned place preference.

2. Results

To evaluate the effect of irregular morphine administration on the acquisition of conditioned place preference, rats were tested for the place preference 24 h after the last conditioning. Time spent in each compartment was recorded under a drug-free situation and time in morphine side was used as an index of place preference. In Fig. 1, it showed the time that each group of rats spent in the drug-paired chamber on the 1st post-conditioning test day. One-way ANOVA showed a significant difference between treatment groups ($F_{(4, 40)}=2.837$; $p<0.05$). The Student–Newman–Keuls *post hoc* comparisons indicated

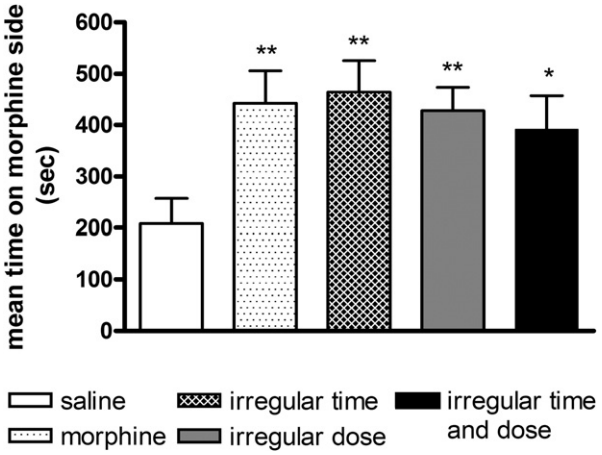

Fig. 1 – Preference for the morphine-associated environment on the test day was induced by 12 days morphine treatment in rats. The figure shows the mean (±S.E.M.) time (s) spent in the drug-paired box during the 15-min no-drug period, 24 h after the last morphine pairing. ANOVA showed that regular morphine ($n=8$), irregular time group ($n=10$), irregular dose group ($n=11$) and irregular time and dose group ($n=8$) spent more time in the morphine paired box compared with the saline control group ($n=8$).$^{*}p<0.05$; $^{**}p<0.01$. No significant difference was found between the three irregular morphine treatment groups and regular morphine treatment group.

that all morphine-treated groups expressed a place preference for the morphine-paired compartment compared to the saline-treated group after the repeated exposures to morphine (Fig. 1), but no significant difference was found between morphine treatment groups ($F_{(3, 33)}=0.134$; $p=$ns). The body-weight data were analyzed with two-way ANOVA, which indicated that body-weight changes of four morphine treatment groups had no significant difference between each other (data not shown).

To further evaluate the effect of irregular morphine administration on the retention of conditioned place preference, rats were retested daily for place preference for another 13 continuous days. We found that the preference index of the regular morphine group decreased from 442±60 s on the first testing day to 380±49 s (which was still much higher than that of the saline group) on the 14th testing day. A two-way repeated ANOVA indicated that there were significant interaction effects of Treatment×Days ($F_{(52, 481)}=1.520$, $p<0.05$), and significant main effects of Treatment ($F_{(4, 40)}=13.060$, $p<0.001$) and Days ($F_{(13, 481)}=7.845$, $p<0.001$). The Student–Newman–Keuls *post hoc* comparisons indicated that morphine-treated rats expressed higher CPP versus saline-treated rats ($p<0.001$, saline group versus regular morphine group, irregular time group and irregular time and dose group; $p<0.01$, saline group versus irregular dose group). When comparing three irregular morphine-treated groups with regular morphine group, significant decrease in the time spent in the morphine-paired compartment was found in irregular dose group and irregular time and dose group ($p<0.01$, regular morphine group versus irregular dose group; $p<0.05$, regular morphine group versus irregular time and

dose group). However, irregular time group showed similar behavioral response to regular morphine group (p=ns), although a trend of potentiated CPP was found during the first 4 days especially on day 4 ($p<0.05$). On the other hand, irregular dose group exhibited decreased place preference compared to irregular time group during morphine cessation ($p<0.05$, Fig. 2). To further evaluate the extinction of CPP in different treated groups, we compared the preference on day 1 and day 14 using a two-way repeated ANOVA. The test days were used as within subject factor and different treatments as between group factor. It was found that there is a significant main effect of test days ($F_{(1, 88)}=18.884$, $p<0.001$). Repeated measures revealed that irregular dose group showed significant less preference for the morphine side on day 14 than day 1 ($F_{(1, 20)}=12.102$, $p<0.01$), whereas other morphine treatment groups did not show significant reduction of the preference on day 14 ($F_{(1, 14)}=1.233$ for regular morphine group; $F_{(1, 18)}=1.56$ for irregular time group; $F_{(1, 14)}=3.112$ for irregular time and dose group, all $p>0.05$). Saline group also showed reduced preference on day 14 ($F_{(1, 14)}=13.851$, $p<0.05$).

Previous evidence indicated that overdose heroin was dangerous to survival (Zador et al., 1996). In the present study, we also recorded the survival rate of animals in each group. The survival rates of the four morphine-treated groups during the morphine conditioning session showed a significant difference (Fig. 3). In regular morphine group, which received morphine regularly, all rats lived throughout the drug conditioning sessions and the drug cessation session (survival rate=100%). However, the survival rate of irregular dose group was lower than 70% at the end of the conditioning session, irregular time group was 85%, and irregular time and dose group was 80%.

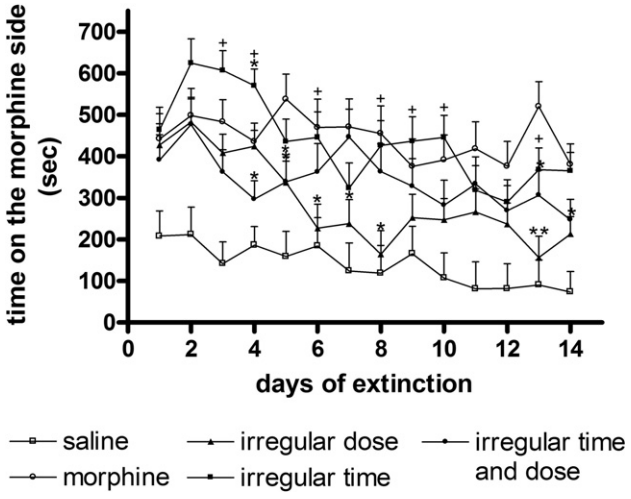

Fig. 2 – Repeated preference tests during the 14-day testing session. All morphine-treated rats showed significant preference for the drug paired chamber compared with the saline control group. The figures show the mean (±S.E.M.) time (s) spent in the drug-paired box during the 15-min no-drug test period of each testing day. Differences of abolishment of place preference were found when three irregular morphine-treated groups were compared with regular morphine group by Student–Newman–Keuls test. *$p<0.05$, **$p<0.01$, versus regular morphine group. +, $p<0.05$, versus irregular dose group.

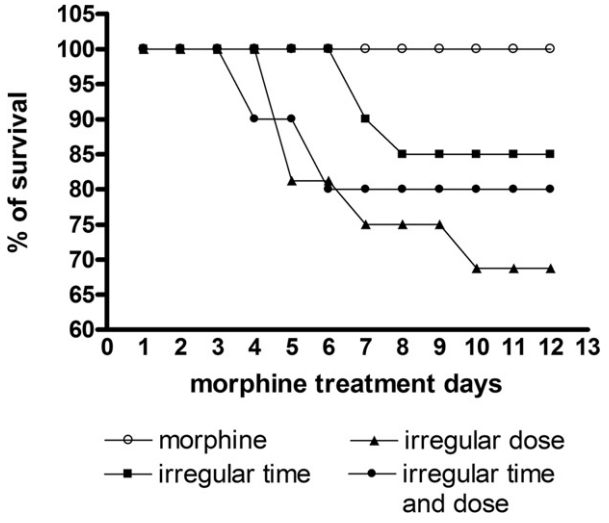

Fig. 3 – The survival rate of each morphine treatment group during the conditioning session is presented. The survival rate of saline control group (data not shown) and regular morphine treatment group are 100% throughout the experimental sessions. At the end of conditioning session, the survival rate of irregular time group, irregular dose group and irregular time and dose group are 85%, 69%and 80%, respectively.

3. Discussion

In the present study, we investigated morphine-induced conditioned place preferences following a variety of pairing patterns in rats. Rats received morphine pairing either regularly or irregularly during the conditioning session. After the same total dose of morphine administration, all rats displayed significant preference for the morphine-paired side. These results indicated that repeated parings of morphine and a specific environment could lead to a place preference regardless of different paring patterns. However, differences in the retention of the preference were revealed among morphine-treated groups. Rats of regular morphine group were the most resistant to the abolishment whereas rats who received variable doses (irregular dose group) during training showed the most rapid preference abolishment. Rats received morphine at the irregular injection time but the same doses (irregular time group) showed potentiated preference during the early morphine cessation period compared with regular morphine group. Thus, the repetition pattern of drug intake played a crucial role in the persistence of morphine-induced place preference.

Irregular time group showed higher preference scores than those in regular morphine group in the first 4 morphine cessation days. However, the preference score decreased to the level of regular morphine group from the 5th morphine cessation day. Thus, training repetition intervals play an important role in classical conditioning in the present study.

This is consistent with previous studies on other kinds of learning which have demonstrated the importance of inter-study intervals for the learning effect (Donovan and Radosevich 1999). Moreover, these results may suggest a potential role of the drug intake pattern in addiction as much of evidence suggesting that addiction represents an abnormality of learning and memory (Hyman, 2005; Kelley, 2004; Zhang et al., 1998). Previous studies showed that circadian time plays a significant role during associative learning between arousing stimulation (rewarding and aversive) and specific context (Ralph et al., 2002; Cain et al., 2004), and this circadian timing system is regulated by the clock genes (Van der Zee et al., 2008). In the present study, all conditioning sessions occurred at two regular timing points and all tests were conducted at one of these two timing points.

In this study we also demonstrated that the preference scores of irregular dose group and irregular time and dose group reduced faster than those in regular morphine group during morphine cessation period. Especially, irregular dose group showed a significantly lower preference compared with regular morphine group from the fifth morphine cessation day. The reason for this facilitation of the preference extinction is unknown, but it may be related to the reward expectation and reward prediction errors theory (Shidara and Richmond, 2002; Sutton and Barto, 1998). According to this theory, animals use previous experience to anticipate the outcomes. Learning occurs when the actual outcome differs from the predicted outcome, resulting in a prediction error. Dopamine neurons were found to play an important role in the predictions of future events, especially in the reward-related predictions. (Schultz et al., 1997). Thus, reward prediction errors lead to modification of the behavioral responses until the outcome can be reliably anticipated. Here, rats in irregular dose group received morphine injections at regular time point but with irregular doses. Since the dose of morphine may represent the intensity of rewarding stimuli (see Experimental procedures and Table 1), the irregular dose of morphine may lead animals into predicting errors and disrupt the morphine-associative memories (Schultz and Dickinson, 2000).

We found that the parallel saline control group shows progressively decreased preference baseline. This may suggest that the conditioned preference we measured is due to not only morphine-related memory but also other psychological processes, for example, loss of the novelty of the compartments. Nonetheless, preference of regular morphine group was much more resistant to distinguish comparing with saline control group. On the other hand, irregular dose group showed more rapidly lose of their conditioned preference.

In the present study, the dosing regime and the number of conditioning trials we used might produce a ceiling effect that masked differences between the groups (Brabant et al., 2005). It was found that the dose and number of drug–context pairings might influence the magnitude and the long-lasting retention of conditioned place preference. Here, the dose of morphine we used was average 10 mg/kg per injection and there were a total of 12 morphine-context pairings during conditioning. Thus, the magnitude and the retention of the conditioned place preference are much stronger than other dosing and injection regimes. Lower doses and less conditioning trials need to be tested in future studies.

Together, we demonstrated that morphine pairing patterns affected the maintenance but not the acquisition of conditioned

Table 1 – The schedules used for group irregular time group.

Injection	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10
1st	m	m	s	m	s	m	m	m	m	m
2nd	m	s	m	m	m	s	s	s	s	s
3rd	s	m	m	m	s	s	m	s	s	m
4th	m	s	s	m	s	m	s	s	m	s
5th	s	m	s	m	m	s	m	m	s	m
6th	m	s	m	s	m	s	s	m	m	s
7th	m	m	s	s	m	s	m	m	m	s
8th	s	s	m	s	s	m	m	s	s	s
9th	m	m	m	s	m	m	s	m	m	m
10th	s	m	s	m	m	m	s	m	s	m
11th	s	s	s	s	m	m	m	s	s	s
12th	s	s	s	s	s	m	m	s	s	s
13th	m	m	m	m	s	s	s	m	m	m
14th	m	s	m	m	m	s	m	s	m	s
15th	s	s	m	m	m	m	s	s	s	m
16th	s	m	m	s	s	s	s	s	m	m
17th	s	s	s	s	s	m	s	s	s	s
18th	m	m	m	s	m	m	m	m	m	m
19th	m	s	s	m	s	s	s	m	m	s
20th	m	s	s	m	s	s	s	s	m	s
21st	s	m	s	s	s	s	m	m	s	m
22nd	s	s	m	s	m	m	s	m	s	s
23rd	s	m	m	m	s	s	m	s	s	m
24th	m	m	s	s	m	m	m	m	m	m

24 injections were performed during the conditioning period. s, injections of saline (10 ml /kg). m, injections of morphine (10 mg /kg). Intervals between morphine injections were randomized.

place preference when the total dose of morphine was the same. Irregular pattern of morphine administration altered the retention of morphine-induced associative memories. This alteration may be due to the influence of pattern of administration on the rewarding effects of morphine. Previous studies also reported that 129/J mice did not develop conditioned place preference after "binge" cocaine administration, but did after a single dose (Zhang et al., 2002). In addition, although our results mainly demonstrate the differences of reward-related learning induced by various repetition patterns, there are many other explanations such as incentive learning and incentive sensitization theories (Robinson and Berridge, 1993).

Furthermore, morphine is a kind of effective analgesics but is limited to special use because of its addictive effect (Harris et al., 1975). Our present results demonstrated that more fragile memories of morphine could be obtained by using irregular doses. Thus, this study might provide new ideas to use morphine appropriately as a widely used sedative drug for the treatment of pain, although more evidence are required to prove these findings (Ziegler, 1997). Analysis of the survival rates of rats indicated that the survival rates of three irregular morphine-treated groups were lower than those of the regular morphine group. The possible reasons are as follows: (1) any contiguous series of unusually high-dose morphine administration is beyond what the rats could withstand. (2) Since rats received morphine irregularly, there might be some other factors such as sensitization, adaptation, and tolerance contributing to deaths (Koob et al., 2004; Stolerman, 1993). Further research is needed to provide more evidence in favor of these findings.

4. Experimental procedures

4.1. *Subjects*

Male adult Sprague–Dawley rats (220–280 g, from Kunming Medical College, China) were housed in a temperature-controlled (23±1 °C) room in a 12-h light/dark cycle (light on 8:00 a.m. to 8:00 p.m.). Food and water were available *ad libitum*. Experiments were conducted in an illuminated house with 60 dB white noises. The room temperature was controlled at 23±1 °C during all experiments. All efforts were made to minimize the pain and discomfort during drug injection (i.p.), e.g. handhold the rats softly for a few minutes before injection. All experimental procedures were approved by the Animal Experimental Committee, Kunming Institute of Zoology, Chinese Academy of Sciences, and were conducted in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals (NIH Guidelines).

4.2. *Drugs suppliers*

In the present study, drug treated rats were injected with morphine-hydrochloride (purchased from Northeast Production Group, Shenyang, China, i.p.). Saline control groups were injected with physiological saline (NaCl 0.9%, i.p.). Morphine-hydrochloride was dissolved in the physiological saline when it was used. We corrected all the morphine doses for salt and water content in the molecule.

4.3. *Experimental design*

Five groups of rats were used in this study: one saline control group (group S) and four morphine treatment groups. Each morphine treatment group of rats received morphine injections daily with either: the same dose at the same time (regular morphine group); the same dose at an irregular injection time (irregular time group, see Table 1); variable doses at the same time (irregular dose group, see Table 2); and irregular doses with irregular injection time (irregular time and dose group). The morphine injection schedules were generated by the computer and selected to avoid too much morphine receiving once or continuously morphine receiving. For irregular dose group, the doses of morphine were between 0 and 20 mg/kg per injection (see Table 1). For irregular time group, schedules were excluded if there were more than five continual injections of morphine or saline (see Table 2). The morphine administration schedule of irregular time and dose group was a combination of the two schedules above. Thus, for irregular time and dose group, we used the administration time in Table 1 and the doses in Table 2. For the regular morphine group, the daily

Table 2 – The schedules used for group irregular dose group.

Injection	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10	Rat 11
1st	12.7	5.5	7.3	14.5	9.0	12.7	3.6	14.5	12.7	5.5	9.0
2nd	0	1.8	11.0	16.4	16.4	20.0	11.0	20.0	20.0	1.8	0
3rd	20.0	14.5	0	11.0	12.7	16.4	9.0	1.8	0	11.0	11.0
4th	18.2	20.0	1.8	18.2	3.6	7.3	5.5	12.7	18.2	20.0	1.8
5th	11.0	16.4	5.5	3.6	14.5	11.0	12.7	5.5	11.0	16.4	5.5
6th	7.2	18.2	18.2	5.5	5.5	0	20.0	9.0	3.6	18.2	3.6
7th	14.5	3.6	20.0	7.3	20.0	9.0	16.4	0	14.5	12.7	20.0
8th	9.0	7.3	3.6	12.7	7.3	5.5	18.2	11.0	9.0	7.3	18.2
9th	3.6	11.0	16.4	0	0	18.2	1.8	7.3	7.2	14.5	16.4
10th	16.4	0	14.5	20.0	18.2	14.5	14.5	18.2	16.4	0	14.5
11th	1.8	9.0	12.7	1.8	11.0	1.8	0	16.4	1.8	9.0	12.7
12th	5.5	12.7	9.0	9.0	1.8	3.6	7.3	3.6	5.5	3.6	7.3

12 morphine injections were performed during the conditioning period at regular time every day (mg/kg). The dose of each injection was irregular (0 to 20 mg /kg).

injection dose was 10 mg/kg. All drug treatment rats received totally the same dose of morphine during the conditioning session (120 mg/kg body weight).

4.4. *Conditioned place preference*

The CPP paradigm consisted of two xylary compartments of equal size (45×45×30 cm), which were separated by a gray interim chamber (45×22.5×30 cm) with two guillotine doors. In order to make the rats distinguish the two conditioning compartments, we made two completely different environments using visual cues and tactile cues. One compartment was painted with black vertical stripes (5 cm wide) on the white walls and had a textured gray floor; the other was painted with horizontal stripes (5 cm wide) and had a smooth gray floor. The intervals between the stripes were 5 cm.

We used an identical CPP procedure to those previously reported (Lei et al. 2005). The experiment included three phases: pre-conditioning phase (1–3 days), conditioning phase (4–15 days) and post-conditioning test phase (16–29 days). During pre-conditioning phase, animals were placed in the center of the interim chamber with two guillotine doors open. They were allowed to explore the entire apparatus for 15 min for the adaptation to this new environment. The time they spent in each chamber was recorded and used as preference baseline. This baseline test was used to reduce the stress associated with the novelty of experimental apparatus and discard the animals that showed extreme preference to any compartment at the beginning. During the conditioning phase (12 days), rats were immediately confined to the morphine side after a morphine injection or to the saline side after a physiological saline injection for 50 min with two guillotine doors closed. The combination of the injections (morphine or saline) and compartments (two sides) was counterbalanced across subjects. We set two injection timings, 8:30 am and 14:30 pm. The intervals were 6 h to make sure that the morphine effect from the previous session does not carry over to the next one. Morphine control group received daily morphine at 8:30 am and saline at 2:30 pm. Saline control group received only saline at the same injection time as the morphine control group. Irregular morphine groups were injected with either saline or morphine (according to the different schedules, see Table 1 and Table 2) at these two timing points each day. The post-conditioning test phase was carried out at least 24 h after the last injection of morphine, all rats were placed in the center of the interim chamber with the doors open and were allowed free access to the apparatus for 15 min. The time they spent in each compartment was recorded during this drug-free test session and used as preference score. Fourteen days of continuous preference tests were performed repeatedly in a drug-free situation. The position of the rat was defined by the position of its body (forelimbs and head) and CPP was demonstrated by the time each rat spent in the morphine-paired and vehicle-paired compartments.

Each rat was weighed daily before injection, so we could treat all of the rats with commensurate doses of morphine and saline according to their body weight. At the same time, we investigated how the body weight changed during the whole experimental period, especially during the morphine cessation period. We also recorded the number of subject in each group as survival index.

4.5. *Statistical analysis*

Place preference of pre-conditioning and post-conditioning test were determined by the absolute time spent in each chamber. Time spent in the morphine-paired compartment during the preference test was expressed as mean±S.E.M. For the 1st day post-conditioning test, data were analyzed using one-way analyses of variance (ANOVAs). For the repeated tests session (14 days), a two-way repeated ANOVA was used to analyze the data with treatment (different injection schedules) as the between-subjects factor, and testing day (14 levels) as the within-subjects factor. Significant main or interaction effects were followed by *post hoc* Student–Newman–Keuls tests. Statistical analyses were conducted using the SPSS 13.0 Statistical Package. Statistical differences of $p<0.05$ were considered significant.

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