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Morphine state-dependent learning: sensitization and interactions with dopamine receptors

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Abstract

In the present study, the effects of morphine sensitization on impairment of memory formation and the state-dependent learning by morphine have been investigated in mice. Pretraining administration of morphine (0.5, 2.5 and 5 mg/kg) dose dependently decreased the learning of a one-trial passive avoidance task. Pretest administration of morphine (0.5, 2.5 and 5 mg/kg) induced state-dependent retrieval of the memory acquired under pretraining morphine influence. Pretraining or pretest administration of naloxone (0.25, 0.5 and 1 mg/kg) reversed both responses to morphine (5 mg/kg). Amnesia induced by pretraining morphine was significantly reversed in morphine-sensitized mice which had previously received once daily injections of morphine [20 and 30 mg/kg, subcutaneously (s.c.)] for 3 days. Morphine sensitization tended to reverse but did not significantly affect morphine state-dependent memory. The inhibition of morphine-induced amnesia in morphine-sensitized mice was decreased by once daily administration of naloxone (0.5, 1 and 2 mg/kg) 30 min prior to injection of morphine (20 mg/kg/day×3 days). Three-days administration of 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine HCL (SKF 38393; 8, 16 and 32 mg/kg) or SCH 23390; *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCL (0.01, 0.05 and 0.1 mg/kg) before morphine (for 3 days) and during morphine-sensitization, decreased and increased, the amnesia induced by pretraining morphine, respectively. Similar administration of quinpirole (0.5, 1 and 2 mg/kg) or sulpiride (25, 50 and 100 mg/kg) before morphine also decreased and increased the amnesia induced by pretraining morphine, respectively. The results suggest that morphine sensitization affects the impairment of memory formation, but not the facilitation of retrieval induced by morphine and thus it is postulated that dopamine receptors may play an important role in this effect.

Keywords: Morphine; Naloxone; Dopamine receptor agonists and antagonists; Sensitization; (Mouse)

1. Introduction

Modulation of learning and memory processes by morphine and other opioidergic agents has been demonstrated in many studies (McGaugh and Baratti, 1985; Ragozzino and Gold, 1994; Vaccarino et al., 1998). Some studies show that morphine can induce dual actions on learning and memory (Shiigi and Kaneto, 1990; Khavandgar et al., 2002). The effects of morphine on memory depend on the timing of drug administration (Nishimura et al., 1990). Pretraining morphine inhibits the acquisition of memory in different paradigms such as y-maze discrimination (Castellano, 1975), active or passive avoidance (Izquierdo, 1979) and operant tasks (Bruins Slot and Colpaert, 1999a), while pretest morphine facilitates memory retrieval in amnesia induced by pretraining administration of morphine (Khavandgar et al., 2002, 2003). This phenomenon is known as morphine state-dependent learning and it has been suggested that it is time- and dose-dependent (Nishimura et al., 1990; Khavandgar et al.,

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2003). "State-dependent learning" denotes the fact that information that has been learned while the animal is under the influence of a certain drug ("state") can only be recalled and used to solve a task when the animal is in the same state in which the information was learned, but not in a different, i.e., undrugged state (Colpaert, 1990; Carlezone et al., 1995).

Repeated administration of opiates with an agonistic action on μ-opioid receptors such as morphine elicits an enhancement of their behavioural effects (Kuribara, 1995; Shippenberg et al., 1996). This phenomenon, known as behavioural sensitization, has been hypothesized to play a role in the development of addiction and especially in the high rate of relapse seen in drug addicts even after very long periods of abstinence (Gaiardi et al., 1991; Spanagel, 1995). This development of behavioural sensitization to opiates in mice is presumed to depend on certain changes in the dopaminergic systems via stimulation of μ-opioid receptors (Kuribara, 1995; Serrano et al., 2002). There is increasing evidence that the mesolimbic dopaminergic pathway plays an important role in sensitization processes (Perugini and Vezina, 1994; Cador et al., 1995). Serrano et al. (2002) suggest that dopamine is involved in the induction of morphine sensitization and that dopamine receptors may be essential in the acquisition and expression of sensitization. It has been reported that both dopamine D1 and D2 receptors have an important role in the acquisition and expression of morphine sensitization in mice (Jeziorski and White, 1995; Serrano et al., 2002).

It has been reported that the activation of μ-opioid receptors plays an important role in morphine state-dependent learning (Saha et al., 1991; Bruins Slot and Colpaert, 1999b). It appears that this kind of learning is related to the reward effects of morphine. Some authors have suggested a functional interrelationship between μ-opioid receptors and dopamine receptors in modulating important central processes, including dependence (McBride et al., 1999), reward-related learning (Beninger and Miller, 1998) and sensitization (Kuribara, 1995). It is well known that learning and memory are critically involved in morphine dependence and relapse (White, 1996) and that morphine plays an important role in sensitization processes (Bartoletti et al., 1987; Jeziorski and White, 1995). We therefore hypothesized that the morphine sensitization may affect the morphine-induced state of memory and that both μ-opioid receptors and dopamine receptors may be involved in this phenomenon. In the present study, the influence of morphine sensitization on the retrieval of a single-trial step-down passive avoidance task learned following morphine administration, either in the presence or in the absence of pretest morphine in mice has been investigated. If our hypothesis was correct, we intended to examine the possible role of dopamine receptor subtypes in this effect. The step-down passive avoidance paradigm used in this study is an accepted model to test long-term memory in a simple conditioning task that is thought to involve the amygdala (Jellestad and Bakke, 1985; Izquierdo et al., 1999).

2. Materials and methods

2.1. Animals

Male albino mice (Pasteur institute; Tehran, Iran) weighing 22–30 g were used. The animals were housed 10 per Plexiglas cage, in a room with controlled photoperiod (a 12-h light/dark cycle) and temperature (22±2 °C). They had food and water available ad lib and were allowed to adapt to the laboratory conditions for at least 1 week before the experiments. Each animal was used once only. All procedures were carried out in accordance with the institutional guidelines for animal care and use.

2.2. Apparatus

The passive avoidance apparatus consisted of a wooden box (30×30×40 cm high) with a steel-rod floor (29 parallel rods, 0.3 cm in diameter, set 1 cm apart). A wooden platform (4×4×4 cm) was set in the center of the grid floor. Intermittent electric shocks (1 Hz, 0.5 s, 40 V DC) were delivered to the grid floor by an insulated stimulator (Grass S44, West Warnick, RI, USA).

2.3. Training

A single-trial step-down passive avoidance task was used. Each mouse was gently placed on the wooden platform. When the mouse stepped down from the platform and placed all its paws on the grid floor, intermittent electric shocks were delivered continuously for 15 s (Hiramatsu et al., 1995). This training procedure was carried out between 10:00 and 15:00 h. At 24-h after training, each mouse was placed on the platform again, and the step-down latency was measured with a stopwatch as passive avoidance behavior. An upper cut-off time of 180 s was set. The retention test was also carried out between 10:00 and 15:00 h.

2.4. Drugs

The drugs used in the study were morphine sulfate (Temad, Tehran, Iran), naloxone hydrochloride (Tolid-Daru, Tehran, Iran), 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SKF 38393), *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH 23390), quinpirole and sulpiride (Sigma, St Louis, CA, USA). All drugs were dissolved in sterile 0.9% saline just before the experiment, except for sulpiride that was dissolved in one drop of glacial acetic acid with a Hamilton micro-syringe and made up to a volume of 5 ml with sterile 0.9% saline and was then diluted to the required volume. Control animals received either

saline or vehicle. Morphine and naloxone were injected subcutaneously (s.c.) and other drugs were administered intraperitoneally (i.p.).

2.5. Drug treatment

Ten animals were used in each experimental group. In experiments where animals received two or three injections, the control groups also received two or three saline injections. The intervals of drug administration were based on previous studies in order to obtain a maximum response (Zarrindast et al., 2002; Khavandgar et al., 2002).

Experiment 1 examined the dose–response of morphine state-dependent learning. One control group received saline (10 ml/kg) 30 min before training and 30 min before testing. Three groups of animals received pretraining morphine (0.5, 2.5 and 5 mg/kg) 30 min before training, followed by pretest saline 30 min before testing (Fig. 1A). Another four groups of animals received a pretraining dose of 5 mg/kg of morphine 30 min before training, followed by pretest administration of either saline or morphine (0.5, 2.5 and 5 mg/kg) 30 min prior to testing (Fig. 1B).

Experiment 2 examined the effect of pretreatment naloxone on the morphine-induced state of memory. Four groups of animals were pretreated with either saline or naloxone (0.25, 0.5 and 1 mg/kg) and after 30 min, they received morphine (5 mg/kg) 30 min before training, followed by pretest administration of saline 30 min prior to testing (Fig. 2, left panel). Another four groups of animals received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest administration of either saline or naloxone (0.25, 0.5 and 1 mg/kg) plus morphine (5 mg/kg), with a 30-min interval and were tested after 30 min (Fig. 2, right panel).

Experiment 3 examined the morphine-induced state of memory in the morphine-sensitized mice. In order to induce sensitization to morphine, the animals received either saline or morphine (10, 20 and 30 mg/kg, s.c.) once daily for 3 days (days 1–3) in the colony room. After 5 days (no drug treatment), the first four groups of animals received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest saline 30 min before testing (Fig. 3A). Another four groups of animals received a pretraining dose of 5 mg/kg of morphine 30 min before training, followed by pretest administration of morphine (5 mg/kg) 30 min prior to testing (Fig. 3B).

Experiment 4 examined the morphine-induced state of memory in animals that had previously received a 3-day morphine treatment regimen in combination with naloxone. Four groups of animals received once daily injections of saline or the opioid receptor antagonist, naloxone (0.5, 1 and

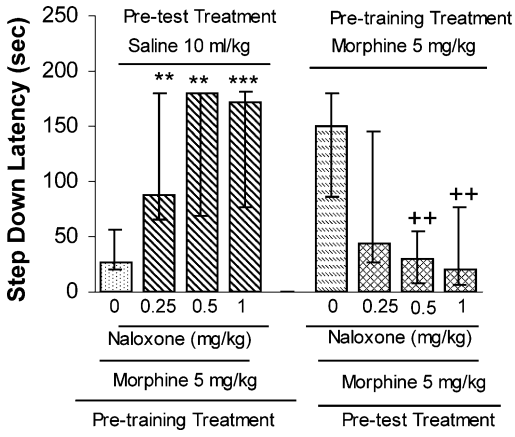

Fig. 2. The effect of naloxone pretreatment on the morphine-induced state of memory. The animals were pretreated with saline or naloxone (0.25, 0.5 and 1 mg/kg) and after 30 min, they received morphine (5 mg/kg) 30 min before training, followed by pretest administration of saline or naloxone plus morphine with a 30-min interval and were tested after 30 min. Each value represents the median and 95% confidence interval of the data from 10 animals. $^{**}P<0.01$; $^{***}P<0.001$, compared to saline/morphine/saline group; $^{++}P<0.01$, compared to saline/saline/morphine group.

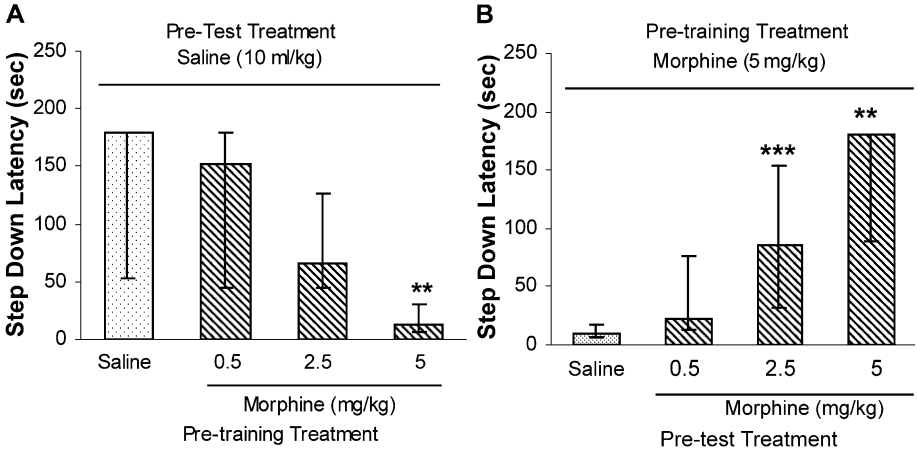

Fig. 1. The effects of pretest administration of saline (A) or different doses of morphine (B) on the step-down latencies of mice trained under the influence of saline or morphine. The animals were trained 30 min after either saline or morphine (0.5, 2.5 and 5 mg/kg, s.c.) and were tested 30 min after receiving either saline or morphine (0.5, 2.5 and 5 mg/kg, s.c.). Each value represents the median and 95% confidence interval of the data from 10 animals. $^{**}P< 0.01$, compared to saline/saline group (A); $^{**}P< 0.01$; $^{***}P< 0.001$, compared to morphine/saline group (B).

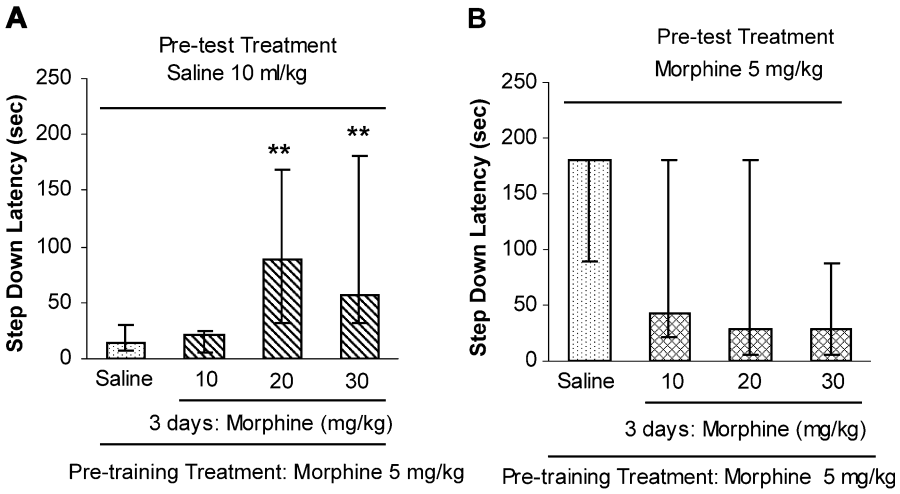

Fig. 3. The effects of morphine sensitization on morphine-induced amnesia and state of memory. In order to induce sensitization to morphine, the animals received morphine (10, 20 and 30 mg/kg, s.c.) once daily for 3 days in the colony room. After 5 days, they received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest saline (A) or morphine (B) 30 min before testing. Two control groups of mice received a once daily injection of saline for 3 days in the colony room. Five days later, they were trained and tested with the other groups. Each value represents the median and 95% confidence interval of the data from 10 animals. $^{**}P<0.01$, compared to saline/saline group.

2 mg/kg), 30 min prior to s.c. injections of morphine (20 mg/kg/day×3 days). After 5 days (no drug treatment), all groups received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest administration of saline 30 min before testing (Fig. 4).

Experiment 5 examined the morphine-induced state of memory in animals that had previously received the 3-day morphine treatment regimen in combination with SKF 38393 or SCH 23390. A lower dose (10 mg/kg) and higher dose (20 mg/kg) of morphine were administered in order to show potentiation and attenuation with dopaminergic agents. Four groups of animals received once daily injections of saline or the dopamine D1 receptor agonist, SKF 38393 (8, 16 and 32 mg/kg), 1 min prior to s.c. injections of morphine (10 mg/kg/day×3 days; Fig. 5, left panel). Another four groups of animals received once daily injections of saline or the dopamine D1 receptor antagonist, SCH 23390 (0.01, 0.05 and 0.1 mg/kg), 60 min prior to s.c. injections of morphine (20 mg/kg/day×3 days) (Fig. 5, right panel). After 5 days, all groups received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest administration of saline 30 min before testing.

Experiment 6 examined the morphine-induced state of memory in animals that had previously received the 3-day

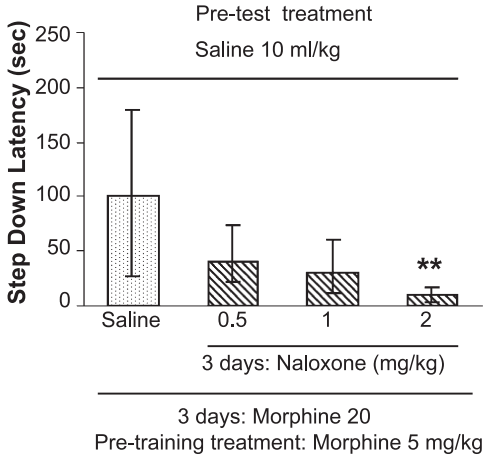

Fig. 4. The effect of naloxone on the inhibition of morphine-induced amnesia in morphine-sensitized mice. The animals received once daily injections of saline or the opioid receptor antagonist, naloxone (0.5, 1 and 2 mg/kg) 30 min prior to s.c. injections of morphine (20 mg/kg/day×3 days). After 5 days, all groups received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest administration of saline 30 min before testing. Each value represents the median and 95% confidence interval of the data from 10 animals. $^{**}P<0.01$, compared to saline/saline group.

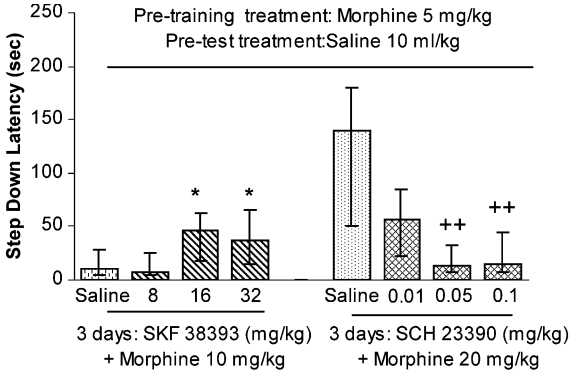

Fig. 5. The effects of SKF 38393 or SCH 23390 on inhibition of morphine-induced amnesia by morphine sensitization. The animals received once daily injections of saline or the dopamine D1 receptor agonist, SKF 38393 (8, 16 and 32 mg/kg), 1 min prior to s.c. injections of morphine (10 mg/kg/day×3 days). Other animals received once daily injections of saline or the dopamine D1 receptor antagonist, SCH 23390 (0.01, 0.05 and 0.1 mg/kg), 60 min prior to s.c. injections of morphine (20 mg/kg/day×3 days). After 5 days, all groups received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest administration of saline 30 min before testing. Each value represents the median and 95% confidence interval of the data from 10 animals. $^{*}P<0.05$, compared to respective saline control group; $^{++}P<0.01$, compared to respective saline control group.

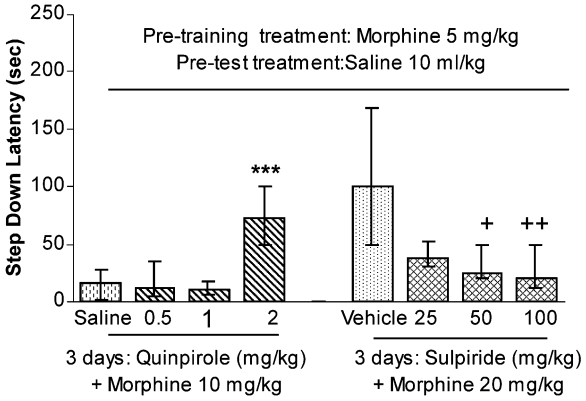

Fig. 6. The effects of quinpirole or sulpiride on inhibition of morphine-induced amnesia by morphine sensitization. The animals received once daily injections of saline or the dopamine D2 receptor agonist, quinpirole (0.5, 1 and 2 mg/kg), 1 min prior to s.c. injections of morphine (10 mg/kg/day×3 days). Other animals received once daily injections of vehicle or the dopamine D2 receptor antagonist, sulpiride (25, 50 and 100 mg/kg), 90 min prior to s.c. injections of morphine (20 mg/kg/day×3 days). After 5 days, all groups received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest administration of saline 30 min before testing. Each value represents the median and 95% confidence interval of the data from 10 animals. ***$P<0.0001$, compared to respective saline control group; $^{+}P<0.05$, $^{++}P<0.01$, compared to respective saline control group.

morphine treatment regimen in combination with quinpirole or sulpiride. Four groups of animals received once daily injections of saline or the dopamine D2 receptor agonist, quinpirole (0.5, 1 and 2 mg/kg), 1 min prior to s.c. injections of morphine (10 mg/kg/day×3 days; Fig. 6, left panel). Another four groups of animals received once daily injections of vehicle or the dopamine D2 receptor antagonist, sulpiride (25, 50 and 100 mg/kg), 90 min prior to s.c. injections of morphine (20 mg/kg/day×3 days) (Fig. 6, right panel). After 5 days, all groups received pretraining morphine (5 mg/kg) 30 min before training, followed by pretest administration of saline 30 min before testing.

2.6. Data analysis

Data are expressed as the median and 95% confidence intervals. All data were analysed by Kruskal–Wallis non-parametric one-way analysis of variance (ANOVA), followed by the Mann–Whitney *U*-test. The latter test was also used where two groups were compared with each other. The criterion for statistical significance was $P<0.05$.

3. Results

3.1. Effect of morphine on memory retention

Fig. 1A shows the effects of pretraining administration of morphine on memory retention. Kruskal–Wallis ANOVA revealed that pre-training morphine (0.5, 2.5 and 5 mg/kg) dose dependently suppressed the learning of a one-trial passive avoidance task [$H(3)=15.65$, $P<0.001$]. Further analysis with the Mann–Whitney *U*-test showed that pretraining morphine (5 mg/kg) impaired the retention latency compared to pretraining saline ($P<0.001$), in animals that were treated pretest with saline.

Fig. 1B shows that animals in which retrieval was impaired due to morphine pretraining administration (morphine-induced amnesia), pretest morphine (0.5, 2.5 and 5 mg/kg) restored the retrieval to the control level (morphine-state of memory) [Kruskal–Wallis ANOVA, $H(3)=19.14$, $P<0.001$]. The maximum restoration was observed with 5 mg/kg of morphine (Mann–Whitney *U*-test, $P<0.001$).

3.2. Effect of naloxone on morphine-induced state of memory

Fig. 2 shows that the inhibitory effect of 5 mg/kg of morphine on memory formation was significantly antagonized by naloxone (0.025, 0.5 and 1 mg/kg) given 30 min before the preraining administration of morphine 30 min before the training trial [Kruskal–Wallis ANOVA, $H(3)=14.31$, $P<0.01$]. The maximum response was obtained with 0.5 mg/kg of naloxone (Mann–Whitney *U*-test, $P<0.001$). In addition, Kruskal–Wallis ANOVA revealed that the pretest administration of naloxone, dose dependently inhibited the restoration induced by 5 mg/kg of morphine [$H(3)=12.99$, $P<0.01$].

3.3. Effects of morphine sensitization on morphine-induced amnesia and morphine-state of memory

As shown in Fig. 3A, amnesia induced by pretraining morphine (5 mg/kg) was significantly inhibited in mice which had previously received once daily injections of morphine (20 and 30 mg/kg, s.c.) for 3 days, compared with mice pretreated with saline [Kruskal–Wallis ANOVA, $H(3)=18.33$, $P<0.001$].

Fig. 3B shows that morphine sensitization in animals which received s.c. injections of morphine (10, 20 and 30 mg/kg) once daily for 3 days did not affect the morphine state-dependent memory of passive avoidance [Kruskal–Wallis ANOVA, $H(3)=2.11$, $P>0.05$].

3.4. Effect of naloxone on inhibition of morphine-induced amnesia by morphine sensitization

Fig. 4 shows the inhibition of morphine-induced amnesia in animals that had previously received the 3-day morphine suppressed by once daily injections of the opioid receptor antagonist, naloxone (0.5, 1 and 2 mg/kg), 30 min prior to s.c. injections of morphine [20 mg/kg/day×3 days; Kruskal–Wallis ANOVA, $H(3)=10.87$, $P<0.05$]. The maximum response was obtained with 2 mg/kg of naloxone (Mann–Whitney *U*-test, $P<0.01$).

3.5. Effects of SKF 38393 or SCH 23390 on inhibition of morphine-induced amnesia by morphine sensitization

Fig. 5 shows that the amnesia induced by pretraining morphine (5 mg/kg) was significantly decreased in animals that had previously received for 3 days SKF 38393 (8, 16 and 32 mg/kg) 1 min prior to s.c. injections of morphine [10 mg/kg/day×3 days; Kruskal–Wallis ANOVA, $H(3)=10.57$, $P<0.05$]. Further analysis with the Mann–Whitney U-test revealed that the higher doses of SKF 38393 (16 and 32 mg/kg) induced this effect ($P<0.05$). In addition, the inhibition of morphine-induced amnesia in animals that had previously received the 3-day morphine was dose dependently suppressed by once daily injections of the dopamine D1 receptor antagonist, SCH 23390 (0.01, 0.05 and 0.1 mg/kg), 60 min prior to s.c. injections of morphine [20 mg/kg/day×3 days; Kruskal–Wallis ANOVA, $H(3)=12.61$, $P<0.01$].

3.6. Effects of quinpirole or sulpiride on inhibition of morphine-induced amnesia by morphine sensitization

Fig. 6 shows that the amnesia induced by pretraining morphine (5 mg/kg) was significantly decreased in animals that had previously received for 3 days dopamine D2 receptor agonist, quinpirole (0.5, 1 and 2 mg/kg), 1 min prior to s.c. injections of morphine [10 mg/kg/day×3 days; Kruskal–Wallis ANOVA, $H(3)=16.03$, $P<0.001$]. Further analysis with the Mann–Whitney U-test revealed that the higher dose of quinpirole (2 mg/kg) induced this effect ($P<0.001$). In addition, the inhibition of morphine-induced amnesia in animals that had previously received the 3-day morphine was dose dependently suppressed by once daily injections of the dopamine D2 receptor antagonist, sulpiride (25, 50 and 100 mg/kg), 90 min prior to s.c. injections of morphine [20 mg/kg/day×3 days; Kruskal–Wallis ANOVA, $H(3)=9.58$, $P<0.05$]. Further analysis with the Mann–Whitney U-test revealed that the higher doses of sulpiride (50 and 100 mg/kg) induced this effect ($P<0.01$).

4. Discussion

In the present study, the effects of morphine sensitization on the morphine-induced state of memory and interactions with dopamine receptor agents in mice were investigated. The step-down passive avoidance paradigm was used for this study. The data indicated that pretraining administration of morphine dose dependently decreased the learning of a one-trial passive avoidance task with a maximum effect of 5 mg/kg of morphine. Pretest morphine administration restored the retrieval to the control level. These effects of morphine that are named state-dependent learning have been demonstrated previously (Nishimura et al., 1990; Bruins Slot and Colpaert, 1999a,b; Homayoun et al., 2003). "Drug-induced state-dependent learning" is used to describe the finding that behavior learned in one drug state is better remembered when retention is tested in the same drug state (Lowe, 1986). Both the inhibition and the restoration of memory by morphine were antagonized by the opioid receptor antagonist, naloxone. In agreement with others (Shiigi et al., 1990; Khavandgar et al., 2002), we showed that μ-opioid receptors are involved in the phenomenon. It has been suggested that morphine affects learning and memory (Castellano, 1975; Izquierdo, 1979; Ukai and Lin, 2002). However, the effect of morphine on memory depends on the dose and the timing of drug treatment; usually, the inhibitory effect is obtained by pretraining trial administration (Nishimura et al., 1990) or after training (Saha et al., 1991). The amnesia induced by morphine can be restored by pretest administration of the opioid (Khavandgar et al., 2002, 2003; Homayoun et al., 2003).

It has been shown that repeated administration of morphine may induce tolerance to its own response (Zarrindast et al., 2002). However, repeated administration of morphine followed by "a period of drug-free treatment" induced sensitization (Jeziorski and White, 1995; Scheggi et al., 2000). Our results showed that the amnesia induced by pretraining morphine was significantly inhibited in morphine-sensitized mice. However, the sensitization tended to decrease restoration of memory retrieval, but did not significantly reduce the behaviour. It has become apparent that the repeated administration of opioids can result in an enhancement of their behavioural effects (Bartoletti et al., 1987; Kalivas and Stewart, 1991). This phenomenon is referred to as sensitization (Robinson and Berridge, 1993; Shippenberg et al., 1996; Scheggi et al., 2000). Although opioid-induced sensitization processes have been described for several behaviours (Kuribara, 1995; Scheggi et al., 2000; Serrano et al., 2002), this had not been shown for learning paradigms.

The inhibition of morphine-induced amnesia in morphine-sensitized animals was decreased by once daily injections of the opioid receptor antagonist, naloxone, for 3 days. Thus, the involvement of μ-opioid receptors in the sensitization processes on impairment of retention by morphine seems likely.

Morphine releases dopamine (Di Chiara and Imperato, 1988; De Fonseca et al., 1995), and therefore, the effects of different dopaminergic agents on morphine-induced amnesia were also investigated in the present study. Dopamine acts through different dopamine receptors including D1, D2 and D3. Many recent experiments show that the dopamine receptor subtypes play an important role in learning processes in various paradigms (see Beninger and Miller, 1998). In addition, it has been reported that chronic treatment with morphine is associated with the development of behavioural supersensitivity mediated by dopamine receptors (Noble and Cox, 1997; Kuribara, 1995). The present results indicate that amnesia induced by pretraining morphine was significantly decreased in the animals that previously received for 3 days either a dopamine D1

receptor agonist, SKF 38393, or a dopamine D2 receptor agonist, quipirole, before morphine administration. The data may suggest that both dopamine D1 and D2 receptors are involved in the morphine-induced sensitization. This is in agreement with data reported by others' report indicating that dopamine may influence the acquisition of sensitization to the motor effects of morphine in mice (Kuribara, 1995). The present results also showed that both the dopamine D1 receptor antagonist, SCH 23390, and the dopamine D2 receptor antagonist, sulpiride, potentiated the morphine-induced amnesia, which may further support the suggestion that a dopamine receptor mechanism is involved in morphine-induced sensitization.

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