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Reversal of morphine-induced memory impairment in mice by withdrawal in Morris water maze Possible involvement of cholinergic system

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Abstract

The effects of morphine and morphine withdrawal on memory performance were examined in mice by using Morris water maze task. Morphine-induced memory impairment at the doses of 5 and 10 mg/kg recovered after repeated administration. Oxotremorine, a muscarinic receptor agonist, at the dose of 0.1 mg/kg ip, and physostigmine, a cholinesterase inhibitor, at the dose of 0.1 mg/kg ip, significantly antagonized morphine (10 mg/kg sc)-induced memory impairment in mice. Furthermore, repeated naloxone (0.5 mg/kg ip) attenuated scopolamine (0.2 mg/kg ip)-induced memory impairment. By using escalating doses of morphine for 13 days, morphine-induced memory impairment was continuously maintained. When withdrawal was precipitated by naloxone (5 mg/kg ip), or administration of oxotremorine (0.1 and 0.2 mg/kg ip) or physostigmine (0.05 and 0.1 mg/kg ip), the impairment was completely reversed. These results suggest that morphine-induced memory impairment could be partially due to the inhibition of the central cholinergic activity. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Morphine; Memory impairment; Naloxone; Oxotremorine; Physostigmine; Morris water maze

1. Introduction

Many reports have demonstrated that acute administration of opioids impairs learning and memory processes (Castellano and Pavone, 1985; Inquierdo, 1980; Itoh et al., 1994; Schulteis et al., 1988; Stone et al., 1991; Walker et al., 1991) and that opioid-induced impairment can be attenuated by naloxone (Canli et al., 1990; Del Cerro and Borrell, 1987; Gallagher, 1982; Introini and Baratti, 1984). On the other hand, the effect of chronic administration of morphine on memory processes is controversial. McNamara and Skelton (1992) reported that repeated exposure to morphine slowed acquisition but did not impair memory retention in water maze task. Sala et al. (1994) and Spain and Newsom (1991) observed that chronic morphine produced a residual working memory impairment in rats and impaired the acquisition of both radial arm maze and Y-maze choice escape, and withdrawal of treatment significantly improved performance of morphine-treated rats in subsequent weeks.

Many investigators have studied the interaction between opioids and the cholinergic system in memory performance. Muscarinic agonists antagonize β-endorphine-induced memory impairment (Introini and Baratti, 1984). Combined administration of oxotremorine and naloxone significantly improves memory function in a one-trial inhibitory avoidance task (Baratti et al., 1984), and the memory-enhancing effect of naloxone can be blocked by the muscarinic antagonist atropine (Baratti et al., 1984). On the contrary, posttraining naloxone reverses scopolamine-induced memory impairment in passive avoidance and spontaneous alternation tests (Rush, 1986; Walker et al., 1991). These observations may suggest that activation of opioid receptors

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inhibit the activity of the cholinergic system and consequently impair memory function.

The Morris water maze is considered as a useful behavioral test for assessing spatial learning ability associated with septohippocampal cholinergic activity (Brandeis et al., 1989; Givens and Olton, 1990; Morris et al., 1982). Although one study indicated that acute morphine impaired the memory function in rats in Morris water maze (McNamara and Skelton, 1992), the intrinsic mechanism was still unclear. In the present study, by using Morris water maze, we examined the memory performance of mice after acute and chronic morphine at an equal daily dose and an escalating dose to investigate how the effect of morphine interacted with the cholinergic system in this spatial performance test.

2. Materials and methods

2.1. Animals and drugs

Male Swiss mice weighing 18–20 g at the start of the experiments were used. They were supplied by the Experimental Animal Center of Shenyang Pharmaceutical University and housed 10 to a cage under a 12-h light–dark cycle and constant temperature (20 ± 2°C) with water and food freely available. Each mouse was used for only one test.

The drugs used were morphine hydrochloride (Shenyang First Pharmaceutical Factory; China), naloxone hydrochloride (Peking Sihuan Pharmaceutical Factory; China), scopolamine hydrobromide, oxotremorine, and physostigmine (Sigma; St. Louis, MO). All the drugs were dissolved in saline.

2.2. Morphine administration

Morphine was administrated at an equal daily dose, 5 or 10 mg/kg. Twenty minutes after injection, the mice were tested. When using an escalating dose regimen, morphine was administered at an interval of 12 h (08:00–20:00 h) for 14 days starting with 10 mg/kg on Day 1. This dose was increased by 10 mg/kg per day until Day 13 when the final dose was 140 mg/kg.

2.3. Motivational test

This experiment was carried out in an iron pool (86 × 17 × 37 cm) filled with clear water to a depth of 20 cm. Water temperature was maintained at 20 ± 0.5°C. At the end of the pool, there was a red platform on which the mice could climb. The location of the platform was made visible by a blue-colored picture mounted above the platform. During the test, the mouse was put into the water at the start point and swam to the end of the pool to climb onto the platform. The swimming time was recorded.

2.3.1. Experiment 1

The mice were tested 20 min after subcutaneous (sc) injection of saline and morphine at the dose of 10 mg/kg.

2.3.2. Experiment 2

The mice were treated subcutaneously with saline or morphine at the dose of 10 mg/kg once a day for 5 days. The mice were tested 20 min after final injection.

2.3.3. Experiment 3

The mice were injected with morphine at escalating dose or saline for 14 days and were tested 20 min after each injection.

2.4. Morris water maze test

The task was carried out as previously described by Watanabe and Satoh (1995). Briefly, a circular pool (diameter 120 cm, height 40 cm) was filled to a depth of 20 cm with water at room temperature (20 ± 0.5°C) and was made opaque by the addition of 15-ml India ink. Four equally spaced points around the edge of the pool were designed as four starting positions: east (E), south (S), west (W), and north (N). An escape platform (diameter 6.5 cm) was set 1 cm below the surface of the water and placed in a constant position in the middle of the SW quadrant. The mouse in the pool was trained to find the platform using a variety of extra-maze cues, including the desk, wall, window, experimenter, etc. The experimenter always sat at the same position.

During the experiment, each mouse was trained four times each day. The mice were placed in the water facing away from the wall from one of four starting sites in a random sequence and each site was used once each day. The latency to find the escape platform was measured manually by clock timer during each trial. Upon finding and climbing the platform, the mice stayed there for 30 s. If the mice failed to find the platform within 60 s, they were placed on the platform by experimenter and a maximum score of 60 s was given. After 30 s rest on the platform, the next trial was initiated.

2.4.1. Administration of morphine at equal daily dose

The task was performed consecutively for 13 days. On Days 1 and 2, each mouse was trained 20 min after saline injection. Every day from Days 3 to 11, the mice in the different groups received morphine (5 and 10 mg/kg sc) 20 min prior to training. On Days 12 and 13, the administration of morphine was eliminated and the mice were trained after administration of saline instead of morphine. Escape latency of each mouse was recorded everyday.

2.4.2. Interaction of oxotremorine or physostigmine with morphine at equal daily dose

The training was carried out consecutively for 5 days. Each group received two injections daily prior to the training. One group received morphine (10 mg/kg sc) + sa-

line (ip) and another group received saline (sc) + oxotremorine (0.1 mg/kg ip)/physostigmine (0.1 mg/kg ip). The third group received morphine (10 mg/kg sc) + oxotremorine (0.1 mg/kg ip)/physostigmine (0.1 mg/kg ip). The blank control group received saline (sc) + saline (ip). Morphine and oxotremorine/physostigmine were given daily 20 min prior to the training. Escape latency of each mouse was recorded everyday.

2.4.3. Interaction of repeated naloxone with scopolamine

The training was carried out consecutively for 5 days. Each mouse received two injections daily prior to the training. One group received scopolamine (0.1 mg/kg ip) + saline (ip) and the second group received saline (ip) + naloxone (0.5 mg/kg ip). The third group received scopolamine (0.1 mg/kg ip) + naloxone (0.1 mg/kg ip). The blank control group received saline (ip) + saline (ip). Morphine and naloxone were given daily 20 and 30 min, respectively, prior to the training. Escape latency of each mouse was recorded everyday.

2.4.4. Administration of morphine at escalating dose

Each mouse was trained 20 min after subcutaneous injection of morphine or saline consecutively for 14 days. On Day 14, the morphine was injected only once at the dose of 75 mg/kg in the morning. The mice were trained 20 min after the morphine injection in the morning. Ten minutes before the training, naloxone (5 mg/kg ip) was given and oxotremorine (0.1 and 0.2 mg/kg ip) or physostigmine (0.05 and 0.1 mg/kg ip) was given 20 min before the training. The blank control group received equal volume of saline. On Days 15 and 16, all mice were tested without giving any drug. Escape latency of each mouse was recorded everyday.

2.5. Statistics

The results were expressed as the mean ± S.E. Data were analyzed using repeated-measures ANOVA or one-way ANOVA followed by the Dunnett's test for comparison between groups. Differences with $P < .05$ were considered statistically significant.

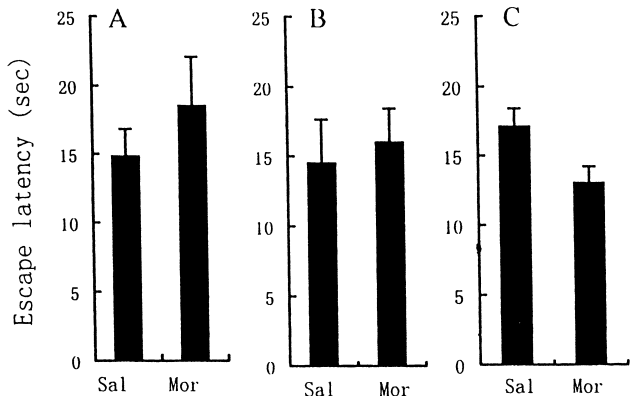

Fig. 1. Effect of morphine on motivational performance of mice. Morphine was administrated at the dose of 10 mg/kg for 1 day (A) or 5 days (B) or at escalating dose (C). Each point represents the mean ± S.E. of 10 mice.

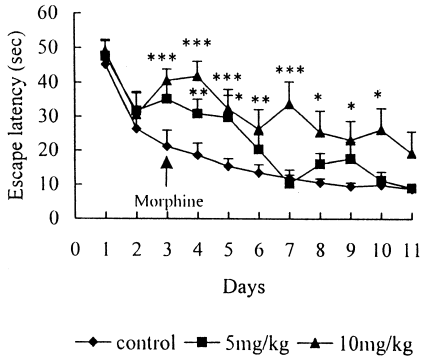

Fig. 2. Effects of morphine at the equal daily doses on spatial memory in Morris water maze in mice. Each point represents the mean ± S.E. of 10 mice. ***$P < .001$, **$P < .01$, *$P < .05$ vs. saline group.

3. Results

3.1. Effect of morphine on motivational performance of mice

The latency of the saline group had no significant difference from that of morphine group at the dose of 10 mg/kg for 1 day (Fig. 1A), 5 days (Fig. 1B), or at escalating dose (Fig. 1C).

3.2. Effect of equal daily doses of morphine on spatial memory

As illustrated in Fig. 2, morphine at the doses of 5 and 10 mg/kg significantly prolonged the escape latencies on Day 3. However, the prolonged latency was significantly shortened from Day 6 in the group of 5 mg/kg [$F(3,35) = 4.63$, $P < .01$] and from Day 11 in that of 10 mg/kg

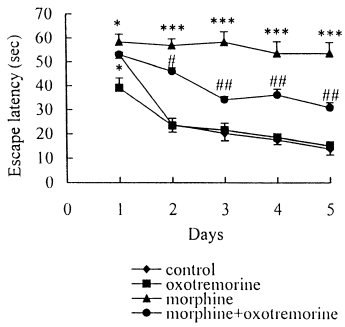

Fig. 3. Oxotremorine (0.1 mg/kg ip) attenuated morphine (10 mg/kg sc)-induced memory deficit in Morris water maze in mice. Each point represents the mean ± S.E. of 10 mice. ***$P < .001$, **$P < .01$ vs. saline group. $^{\#\#}P < .01$, $^{\#}P < .05$ vs. morphine group.

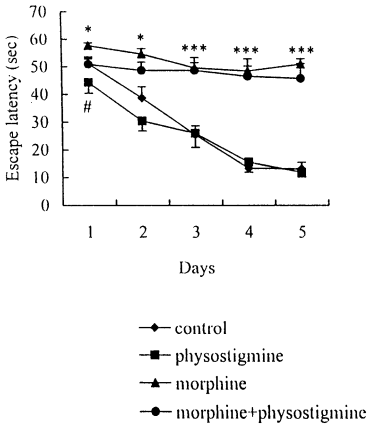

Fig. 4. Physostigmine (0.1 mg/kg ip) attenuated morphine (10 mg/kg sc)-induced memory deficit in Morris water maze in mice. Each point represents the mean ± S.E. of 10 mice. ***$P<.001$, **$P<.01$ vs. saline group. #$P<.05$ vs. morphine group.

[$F(3,35)=20.29$, $P<.001$]. However, on Days 12 and 13, when morphine administration was eliminated, the prolonged latencies were sharply shortened [on Day 12, $F(3,35)=2.25$, $P<.05$ vs. saline group, $F(1,16)=38.9$, $P<.001$ vs. Day 11; on Day 13, $F(3,35)=2.16$, $P>.05$ vs. saline group, $F(1,16)=37.4$, $P<.001$ vs. Day 11).

3.3. Effect of oxotremorine and physostigmine on memory deficit induced by morphine at equal daily dose

The results are shown in Figs. 3 and 4. From Days 1 to 5, the mice with morphine had markedly longer latencies than that of the saline group ($P<.01$). On Day 1, the mice receiving oxotremorine had significant shorter latencies than those receiving saline [$F(3,35)=8.6$, $P<.001$], suggesting that oxotremorine itself has a significant improving effect on spatial memory. From Days 2 to 5, the latencies in mice treated with morphine–oxotremorine were significantly shortened when compared with those treated with morphine–saline [on Day 2, $F(3,35)=3.25$, $P<.05$; on Day 3, $F(3,35)=2.9$, $P<.05$; on Day 4, $F(3,35)=2.3$, $P<.05$; on Day 5, $F(3,35)=3.2$, $P<.05$], which suggests that morphine-induced memory deficit is significantly improved by oxotremorine. The mice treated with physostigmine had significant shorter latencies than those the saline group on Day 1 [$F(3,36)=2.16$, $P<.05$]. However, repeated measures of ANOVA (treatment × time) demonstrated that physostigmine lost its antagonistic effect with the following drug administration [$F(4,36)=2.05$, $P>.05$].

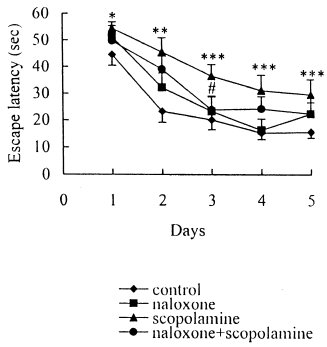

Fig. 5. Repeated naloxone (0.5 mg/kg ip) attenuated scopolamine (0.2 mg/kg ip)-induced memory deficit in Morris water maze in mice. Each point represents the mean ± S.E. of 10 mice. ***$P<.001$, **$P<.01$ vs. saline group. #$P<.05$ vs. scopolamine group.

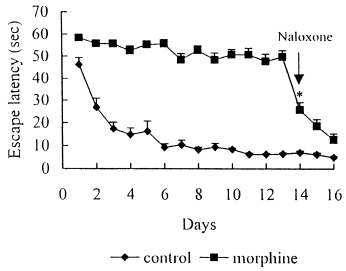

Fig. 6. Effect of naloxone (5 mg/kg ip) on memory impairment induced by morphine at escalating doses in Morris water maze in mice. Each point represents the mean ± S.E. of 10–12 mice. *$P<.05$ vs. morphine group.

3.4. Effect of repeated naloxone on scopolamine-induced memory deficit

As shown in Fig. 5, on Days 1 to 5, mice receiving scopolamine–saline showed longer latencies than those the saline–saline group. The prolonged latency induced by scopolamine could not be shortened by a single treatment with naloxone [on Day 1, $F(3,36)=2.9$, $P>.05$; on Day 2,

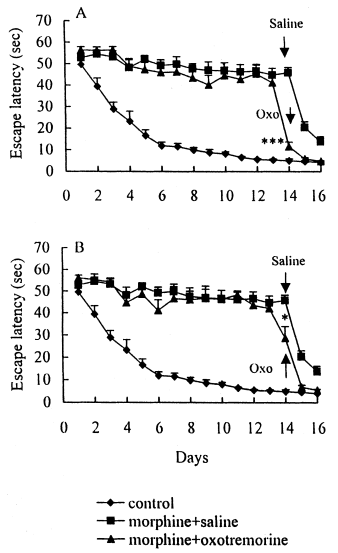

Fig. 7. Effect of intraperitoneal (ip) administration of oxotremorine 0.1 (A) and 0.2 mg/kg (B) on memory impairment induced by morphine at escalating doses in Morris water maze in mice. Each point represents the mean ± S.E. of 19 mice. ***$P<.001$, *$P<.05$ vs. morphine group.

$F(3,36) = 3.8$, $P > .05$]. However, repeated measures of ANOVA (treatment × time) demonstrated that the latency in the scopolamine–naloxone group was significantly shorter than that in the scopolamine–saline group [$F(4,36) = 3.97$, $P < .05$], which suggests that repeated administration of naloxone can antagonize the scopolamine-induced impairment in Morris water maze in mice.

3.5. Effect of naloxone on spatial memory impairment induced by morphine at escalating doses

As shown in Fig. 6, from Days 1 to 13, the mice with chronic morphine at escalating doses had markedly longer latencies than that of the saline group [all $F(1,22) > 14.1$, all P-values $< .001$]. On Day 14, when withdrawal was precipitated by naloxone, the prolonged latencies were markedly shortened [on Day 14, $F(1,22) = 35.3$, $P < .001$ vs. saline group; $F(1,20) = 6.96$, $P < .01$ vs. Day 13].

3.6. Effect of oxotremorine and physostigmine on memory impairment induced by morphine at escalating doses

As shown in Figs. 7 and 8, from Days 1 to 13, the mice with chronic morphine at escalating doses had markedly longer latencies than that of the saline group [all $F(1,22) > 14.1$, all P-values $< .001$]. On Day 14, the prolonged latencies were markedly shortened after injection of oxotremorine 0.1 mg/kg [Fig. 7A; on Day 14, $F(2,26) = 113.0$, $P < .001$ vs. saline group; $F(1,18) = 37.4$, $P < .001$ vs. Day 13] and 0.2 mg/kg [Fig. 7B; on Day 14, $F(2,26) = 32.7$, $P < .001$, vs. saline group; $F(1,18) = 5.37$, $P < .05$ vs. Day 13] or after injection of physostigmine 0.05 mg/kg [Fig. 8A; on Day 14, $F(2,27) = 58.1$, $P < .001$ vs. saline group; $F(1,20) = 14.4$, $P < .05$ vs. Day 13] and 0.1 mg/kg [Fig. 8B; on Day 14, $F(2,28) = 93.2$, $P < .001$ vs. saline group; $F(1,21) = 107.8$, $P < .001$ vs. Day 13].

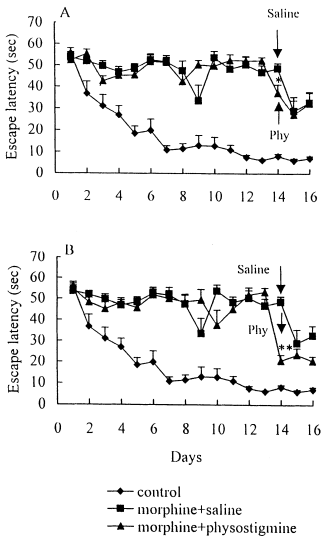

Fig. 8. Effect of intraperitoneal administration of physostigmine 0.05 (A) and 0.1 mg/kg (B) on memory impairment induced by morphine at escalating doses in Morris water maze in mice. Each point represents the mean ± S.E. of 10–11 mice. $^{**}P < .01$, $^{*}P < .05$ vs. morphine group.

4. Discussion

Previous studies have indicated that morphine impaired memory acquisition in the shuttle avoidance test (Inquierdo, 1980), radial maze (Spain and Newsom, 1991), and water maze (Sala et al., 1994). The present study has found that morphine also impaired spatial memory acquisition in Morris water maze at both equal daily dose and the escalating dose regimens. Because there was no significant difference between groups in the motivational test, the observed latency difference in the Morris water maze could not be explained by the effect of morphine on motor function. The present results showed that the memory deficit induced by low doses of morphine was recovered following repeated administration of morphine. Some studies have demonstrated that tolerance development to morphine could be observed in analgesia test at the dose of 5 and 10 mg/kg (Kolesnikov et al., 1992; Trujillo and Akil, 1991). Thus, the memory-recovering phenomenon observed in morphine groups might be related to tolerance development to morphine after prolonged treatment.

It is known that there exists an interaction between opioid and the cholinergic systems (Introini and Baratti, 1984; Rush, 1986; Walker et al., 1991). Some studies have demonstrated that opioid agonists such as morphine and β-endorphine, possessing higher affinity for μ-opioid receptors, inhibit cholinergic activity in the hippocampus (Decker and McGaugh, 1991). Moreover, it is also reported that μ and δ receptors locate on cholinergic terminals, which are normally under tonic inhibition by the opiate system (Heijna et al., 1990). After chronic morphine treatment, opioid receptors responsible for the inhibitory effect may become tolerant to morphine and consequently, the cholinergic neurons are disinhibited (Imperato et al., 1996; Itoh et al., 1994). In the present study, by using Morris water maze, we found that single treatment with oxotremorine significantly improved spatial memory performance, and morphine-induced memory deficit was significantly antagonized by oxotremorine. We also observed that naloxone attenuated the scopolamine-induced spatial memory impairment, which is consistent with previous reports (Rush, 1986; Walker et al., 1991), indicating that naloxone attenuated scopolamine-induced impairment of inhibitory avoidance behavior and spontaneous alternation performance. The naloxone reversal of the behavioral effects of the cholinergic antagonist scopolamine is probably explained by the fact that naloxone may release medial septal cholinergic neurons from opiate inhibition, thereby increasing the release of acetylcholine in the hippocampus, a brain area in which manipulations have profound effects on spatial memory (Barnes, 1988). Thus,

it is possible that the release of cholinergic activity due to opiate tolerance produces the memory-recovering effect in Morris water maze.

Chronic administration of morphine at escalating doses, which would mimic the dosage used by drug addicts to maintain subjective reward properties (Rada et al., 1996), significantly impaired spatial memory in the present study. Reports have demonstrated that opioids impaired memory function through the mediation of μ-opioid receptors (Mauk et al., 1982; Spain and Newsom, 1991; Ukai et al., 2000) and this action of opioids could be reversed by μ-receptor antagonist naloxone (Mauk et al., 1982). Similarly, we have observed that morphine-induced memory deficit was abruptly reversed by naloxone, indicating that restore of the memory function by naloxone is the result of reversal of morphine effects by blockade of μ-receptors. In addition, naloxone should also induce some behavioral withdrawal symptoms, such as jumping, in morphine-dependent mice. However, these symptoms were not clearly observed because the mice were forced to swim to locate the platform in Morris water maze. It is possible that some of the withdrawal symptoms will be masked in such experimental conditions.

Morphine-induced memory deficit was also abruptly reversed by oxotremorine, a cholinergic agonist, or physostigmine, a cholinesterase inhibitor. Similar result (Introini and Baratti, 1984) has been shown that oxotremorine and physostigmine significantly attenuated the β-endorphine-induced impairment of retention of an inhibitory avoidance task in mice. These results may indicate that activation of the cholinergic system produces a similar effect to that of naloxone in reversing the memory impairment induced by opioids. It has been shown that some symptoms of naloxone-precipitated withdrawal could be mimicked by administration of cholinergic agents (Katz and Valentino, 1984; Valentino and Aston-Jones, 1983), and cholinergic antagonists were capable of partial blockade of behavioral withdrawal symptoms of morphine (Buccafusco, 1991; Holland et al., 1993). Smith et al. (1984) reported that muscarinic receptor densities were decreased in the frontal cortex during morphine self-administration. Thus, the present study further confirmed that activation of cholinergic function could overcome morphine-induced memory impairment.

Although the above evidence has implicated a close correlation between the opioid and cholinergic systems, the exact mechanism of their interaction is still not clear. Studies by using in vivo microdialysis have revealed that acute morphine significantly decreased release of acetylcholine in some brain regions (Arenas et al., 1990; Beani et al., 1982; Lapchak et al., 1989; Mulder et al., 1984, 1989; Rada et al., 1991a). The decrease of acetylcholine release induced by morphine in the nucleus accumbens recovered after repeated administration of equal daily dose of morphine for 1 week (Rada et al., 1991b). When using an escalating dose paradigm, morphine retains its capacity to significantly lower extracellular acetylcholine in the nucleus accumbens, and during the morphine withdrawal, acetylcholine release markedly increased in both the nucleus accumbens and the prefrontal cortex (Rada et al., 1996). In the present experiments, it was observed that in Morris water maze, acute morphine impaired memory performance and the impairment recovered after repeated administration of equal daily dose of morphine. Morphine at an escalating dose significantly impaired memory performance and the impaired memory was abruptly reversed by naloxone-precipitated withdrawal from morphine. All these behavioral changes are parallel with the extracellular acetylcholine changes after morphine treatment observed in the microdialysis study (Rada et al., 1996).

However, it is also possible that morphine-modulating memory process is mediated in ways other than through direct opiate–cholinergic interaction. For example, it has been reported that glucocorticoids and their receptors are involved in memory improvement (Roozendaal, 2000; Yau et al., 1999). A 4-day treatment with increasing doses of morphine increases the plasma corticosterone concentration, and after chronic morphine, withdrawal by naloxone, corticosterone secretion is increased (Budziszewska et al., 1999; Milanes et al., 1998).

Taken together, our observations further suggest that morphine-induced memory impairment is closely related to its inhibitory effect on cholinergic function. Naloxone may release cholinergic neurons in the medial septum from opiate inhibition, thereby increasing the release of acetylcholine in the hippocampus, which is associated with spatial memory (Walker et al., 1991). Thus, drugs that can block opioid receptors, or activate cholinergic function, either by directly activating muscarinic receptors, or by increasing synaptic concentrations of acetylcholine, may be useful in reversing morphine-induced memory dysfunction.

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