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Influence of central administration ATP-dependent K^+ channel on morphine state-dependent memory of passive avoidance

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Abstract

Pre-training injection of a moderate dose of morphine (5–10 mg/kg) in a step-down passive avoidance task induced state-dependent learning with impaired memory retrieval on the test day. The impairment of memory was restored after the pre-test administration of the same dose of the drug. We have studied the effect of intracerebroventricular administration of naloxone and K_{ATP} channel modulators (glibenclamide and diazoxide) on the test day on restoration of memory by morphine in mice. The effect of scopolamine on restoration of memory on the test-day by glibenclamide was studied as well. Naloxone pretreatment (0.006, 0.025 and 0.1 μg/mouse) reversed the effect of pre-test morphine administration. The K_{ATP} channel blocker, glibenclamide (0.1, 0.5 and 1 μg/mouse), showed effects similar to those of pre-test administration of morphine. Glibenclamide tended to potentiate the morphine response. Scopolamine (0.15 and 0.30 μg/mouse) prevented the effect of glibenclamide on the restoration of memory. The pre-test administration of different doses of diazoxide (1.7, 5 and 15 μg/mouse), a K_{ATP} channel opener, showed no effect on restoration of memory when used alone but decreased morphine state-dependence. Diazoxide blocked the effects of glibenclamide on memory restoration. It is concluded that K_{ATP} channel modulators may be involved, at least in part, in morphine state dependence through a cholinergic system mechanism.

Keywords: Morphine; Memory; Passive avoidance; Intracerebroventricular; K_{ATP} channel modulators; Scopolamine; (Mouse)

1. Introduction

Learning and memory in laboratory animals are known to be affected by opioids and their antagonists (Izquierdo, 1979; Ukai and Lin, 2002). A method based on the measurement of step-down latency in passive avoidance has been developed for the study of learning and memory in mice (Kameyama et al., 1986). Moderate doses of morphine (5–10 mg/kg) are shown to have an impairing effect on passive avoidance tasks when used pre- or post-training (Castellano, 1975; Izquierdo, 1979; Bruins Slot and Colpaert, 1999a, b). The latency is reduced by pre-training beta-endorphin treatment (Izquierdo and Dias, 1983a; De Almeida and Izquierdo, 1984; Izquierdo et al., 1985) and restored by the same dose of the drug when administered 24 h later in the pre-test session (Izquierdo and Dias, 1983b). Not only beta-endorphin but also the pre-test administration of the same dose of morphine reversed the morphine-induced memory impairment. This is known as state dependence (Nishimura et al., 1990; Bruins Slot and Colpaert 1999a, b) and is believed to involve, in the case of morphine, the activation of μ receptors in the course of training and test session (Shiigi et al., 1990; Bruins Slot and Colpaert 1999a,b). The same authors have suggested that mu but not delta or kappa opioid receptors are involved in morphine state dependence.

Potassium channels represent the largest family of ion channels. Among different types of K^+ channels, K_{ATP} channels are involved in several physiological functions. Ghelardini et al (1998) have demonstrated that the administration of potassium channel openers provokes amnesia in the mouse passive avoidance test and the potassium channel blockers were able to prevent drug-induced amnesia. Stefani et al (1999) have demonstrated that glucose enhances memory in laboratory animals.

Abbreviations: μ, mu; κ, kappa; δ, delta.

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They have suggested that this effect is exerted via modulation of K_{ATP} channels. The same authors have demonstrated that glibenclamide enhances plus-maze spontaneous alternation performance and attenuates the impairing effects of morphine on Y-maze spontaneous alternation. The involvement of K_{ATP} channels in the memory processes was confirmed by other investigators (Inan et al., 2000; Rashidi-Pour, 2001). Morphine has been shown to open K^+ channels and to close Ca^{2+} channels in neurons (Werz and MacDonald, 1983; North, 1989). Several studies suggested that K_{ATP} channels are involved in the central nervous system and in the peripheral actions of morphine (Ocana et al., 1990; Narita et al., 1992a,b; Alarcon et al., 1995; Poggioli et al., 1995; Liang and Gross, 1999; Cohen et al., 2001; Gonzalez et al., 2001). The results of the above investigations support the hypothesis that the action of morphine on μ-opioid receptors is at least partly K_{ATP} channel-dependent.

In the present work we studied the effect of pre-test intracerebroventricular administration of different doses of diazoxide (a K_{ATP} channel opener) and glibenclamide (a K_{ATP} channel blocker) on morphine state-dependence of memory in mice. After the preliminary results had demonstrated that glibenclamide mimicked the effect of pre-test morphine administration, to explore the possible involvement of the cholinergic system, we studied the effect of scopolamine on restoration of memory by glibenclamide. The effect of naloxone on morphine state dependence was also studied.

2. Materials and methods

2.1. Subjects

Male albino NMRI mice weighing 20–30 g were used. The animals were kept in an animal house with a 12-h light/12-h dark cycle and controlled temperature (22 ± 2 °C). They had ad libitum access to food and water and were housed in groups of 10 in Plexiglas animal cages. Each animal was used once. All procedures were carried out in accordance with institutional guidelines for animal care and use.

2.2. Drugs

Morphine sulfate and scopolamine were purchased from Temad (Tehran, Iran). Naloxone hydrochloride was a gift from Tolid-daru (Tehran, Iran). Glibenclamide was a gift from Chemidaru (Tehran, Iran). Sodium pentobarbital was purchased from Sigma (St. Louis, MO, USA). Drugs were dissolved in 0.9% saline except glibenclamide and diazoxide, which were dissolved in water/dimethylsulfoxide (9:1) solvent. Drugs were given by the intracerebroventricular (i.c.v.) route in the right cerebroventricle 5 μl/mouse or subcutaneously (s.c.) in a volume of at most 10 ml/kg.

2.3. Apparatus

The passive avoidance apparatus consisted of a wooden box ($30 \times 30 \times 40$ cm high) with a steel-rod floor (29 parallel rods, 0.3 cm in diameter set 1 cm apart). A wooden platform ($4 \times 4 \times 4$ cm) was set in the center of the grid floor. Intermittent electric shocks (1 Hz, 0.5 s and 50 V DC) were delivered to the grid floor by an insulated stimulator (Grass S44, USA).

2.4. Training

Each mouse was gently placed on the wooden platform. When the mouse stepped down from the platform and placed its paws on the grid floor, intermittent electric shocks were delivered continuously for 15 s (Hiramatsu and Kameyama, 1995). This training procedure was carried out between 10:00 a.m. and 3:00 p.m. Twenty-four hours after training, each mouse was placed on the platform again, and the step-down latency was measured with a step-watch as passive avoidance behavior. An upper cut-off time of 300 s was set. The retention test was also carried out between 10:00 a.m. and 3:00 p.m.

2.5. Intracerebroventricular cannulation and injection

Each mouse was anaesthetized with an intraperitoneal injection of sodium pentobarbital, 60 mg/kg, and its head was oriented in a stereotaxic instrument so that the plane formed by the frontal and parietal bones was parallel to the instrument tabletop. A 23-gauge stainless-steel cannula was positioned above the right lateral cerebral ventricle (AP, −0.9 mm; LAT, 1.4 mm to the bregma; HOR, −2.0 mm to the dura mater). Treatments were delivered i.c.v. in 5 μl using a 30-gauge injection cannula and a Hamilton syringe. Injecting a similar volume of 1% methylene blue solution and determining the distribution of the injected dye in the ventricular space or in the spinal cord identified the injection sites. The i.c.v. injection was distributed through the ventricular spaces and reached the ventral surface of the brain as well as the upper cervical portion of the spinal cord.

2.6. Drug treatment

Fifteen animals were used in each experimental group. For subcutaneous injections the doses were adjusted so that each animal received a volume of at most 10 ml/kg.

2.6.1. Experiment 1

In experiment 1, one group of animals received saline (10 ml/kg) 30 min before training and saline or morphine (5 mg/kg, s.c.) 30 min before testing. The other groups of animals in this experiment were trained 30 min after morphine (5 mg/kg, s.c.) and were tested 30 min after pre-test saline or morphine (5 mg/kg, s.c.) injection.

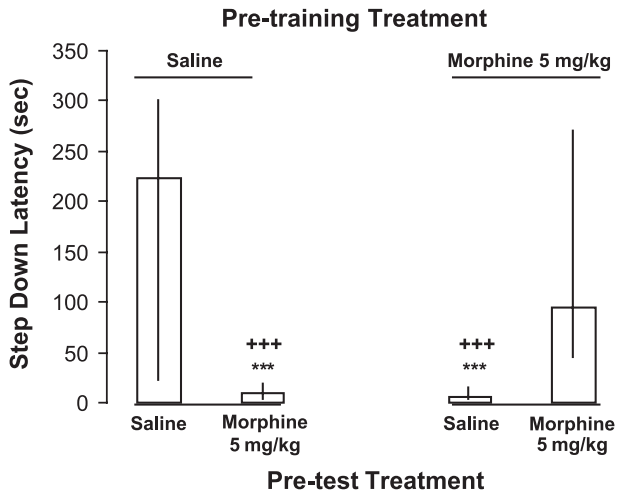

Fig. 1. The effects of pre-training and pre-test administration of morphine or saline on the step-down latencies. The control group received saline (10 ml/kg) 30 min before training and 30 min before testing. Other groups of animals were trained 30 min after morphine (5 mg/kg, s.c.) and were tested 30 min after pre-test saline or morphine (5 mg/kg. s.c.) injection. Each value represents the median and quartile for 15 animals. ***$P<0.001$ compared to pre-training and pre-testing saline, +++$P<0.001$ compared to pre-training and pre-testing morphine (5 mg/kg, s.c.).

2.6.2. Experiment 2

In experiment 2, all animals received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, animals received saline or naloxone (0.006, 0.025 and 0.1 μg/mouse, i.c.v.) 5 min, and in the presence or absence of morphine (5 mg/kg, s.c.), 30 min before testing.

2.6.3. Experiment 3

In experiment 3, all animals received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, the animals received glibenclamide vehicle or glibenclamide (0.1, 0.5 and 1 μg/mouse, i.c.v.) 10 min before testing in the presence or absence of morphine (5 mg/kg, s.c.), 30 min before testing.

2.6.4. Experiment 4

In experiment 4, all animals received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, the animals received diazoxide vehicle or diazoxide (1.7, 5 and 15 μg/mouse, i.c.v.) 10 min before testing in the presence or absence of morphine (5 mg/kg, s.c.), 30 min before testing.

2.6.5. Experiment 5

In experiment 5, all groups received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, the animals received diazoxide vehicle or diazoxide (1.7, 5 and 15 μg/mouse, i.c.v.) 12 min before testing, in the presence of glibenclamide (3 μg/mouse, i.c.v.), 10 min before testing.

2.6.6. Experiment 6

In experiment 6, all groups received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, the animals received saline or scopolamine (0.15 and 0.3 μg/mouse, i.c.v.) 12 min before testing, in the presence of glibenclamide (3 μg/mouse, i.c.v.), 10 min before testing.

2.7. Data analysis

The retention latencies are expressed as the median and interquartile range. The data were analyzed using the Kruskal–Wallis non-parametric one-way analysis of variance (ANOVA) followed by a two-tailed Mann–Whitney's *U*-test, then Holm's Bonferoni correction for the paired comparisons. In all statistical evaluations $P<0.05$ was used as the criterion for statistical significance.

3. Results

3.1. Morphine state of memory and the effect of naloxone

Fig. 1 indicates that morphine injected 30 min before training impaired retention (Mann–Whitney's *U*-test, $P<0.001$). The same drug injected 30 min before testing partially reversed the impairing effect of morphine (5 mg/kg, 30 min before training) (Mann–Whitney's *U*-test, $P<0.001$). (morphine state-dependency).

Fig. 2 indicates that naloxone injected 5 min before testing could not reverse the memory impairing effect of morphine (5 mg/kg, 30 min before training) but decreased the morphine state dependence in a dose-dependent fashion ($H(3)=42.18$, $P<0.001$).

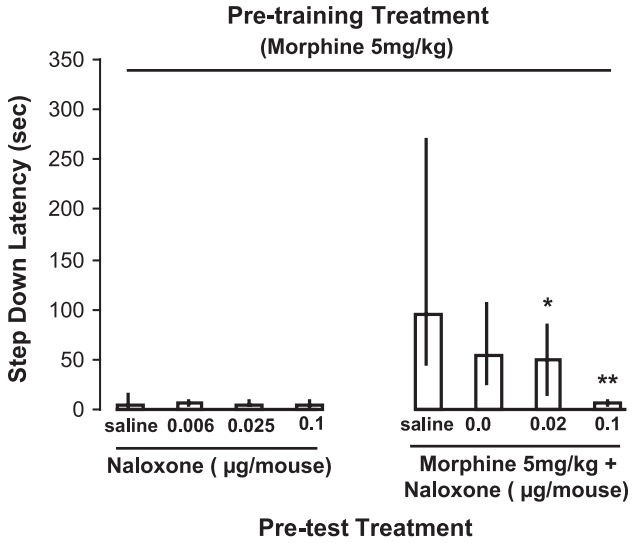

Fig. 2. The effect of pre-test administration of different doses of naloxone with or without morphine on the step-down latencies compared to pre-training morphine and pre-test saline/morphine groups. All animals received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, animals received saline or naloxone (0.006, 0.025 and 0.1 μg/mouse, i.c.v.) 5 min before testing, in the presence or absence of morphine (5 mg/kg, s.c.) 30 min before testing. Each value represents the median and quartile for 15 animals. *$P<0.05$ compared to pre-training and pre-test morphine. **$P<0.01$ compared to pre-training and pre-test morphine.

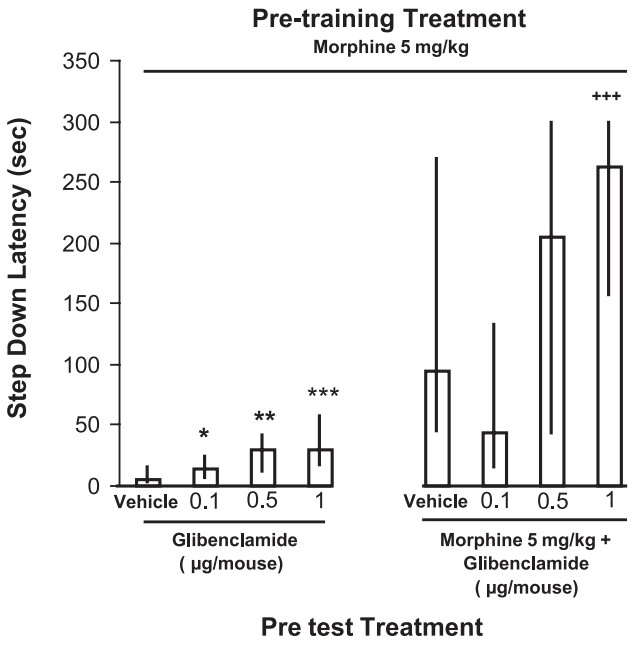

Fig. 3. The effect of pre-test administration of different doses of glibenclamide with or without morphine on the step-down latencies compared to pre-training morphine and pre-test glibenclamide vehicle or morphine groups. All animals received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, animals received glibenclamide vehicle or glibenclamide (0.1, 0.5 and 1 µg/mouse, i.c.v.) 10 min prior to the test session in the presence or absence of morphine (5 mg/kg, s.c.) 30 min before testing. Each value represents the median and quartile for 15 animals. $*P<0.05$ $**P<0.01$, $***P<0.001$ compared to pre-test vehicle control, $+++P<0.001$ compared to pre-training and pre-testing morphine group.

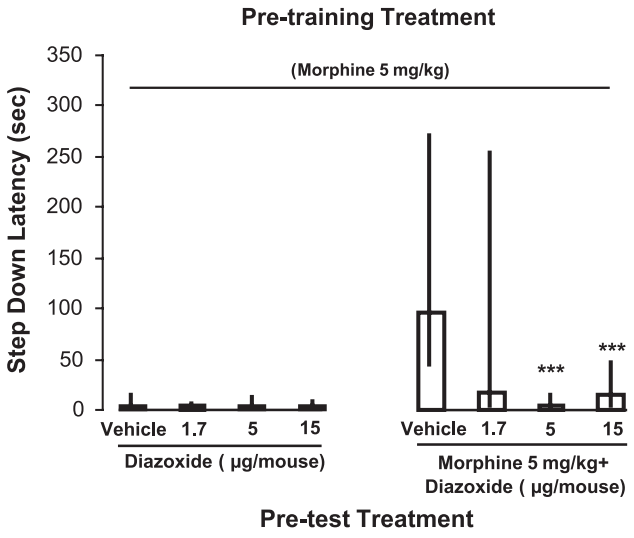

Fig. 4. The effect of pre-test administration of different doses of diazoxide with or without morphine on the step-down latencies compared to pre-training morphine and pre-test diazoxide vehicle or morphine groups. All animals received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, the animals received diazoxide vehicle or diazoxide (1.7, 5 and 15 µg/mouse, i.c.v.) 10 min prior to the test session in the presence or absence of morphine (5 mg/kg, s.c.) 30 min before the test. Each value represents the median and quartile for 15 animals, $***P<0.001$ compared to pre-training and pre-test morphine group.

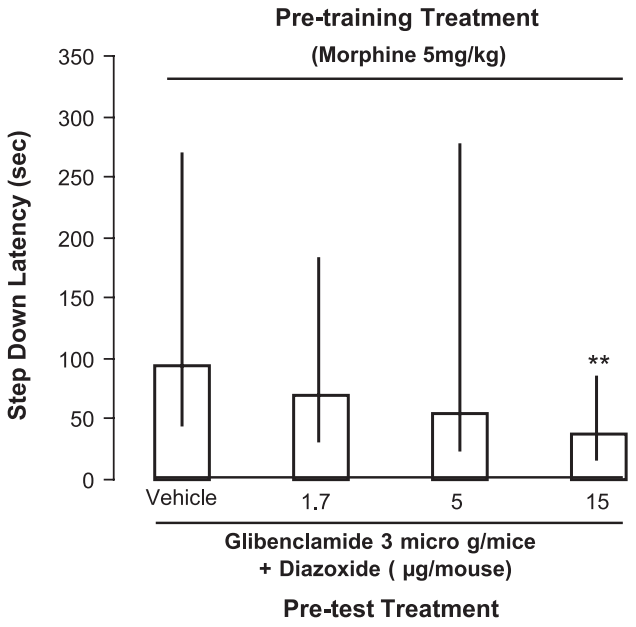

Fig. 5. The effect of pre-test administration of different doses of diazoxide on the step-down latencies compared to the pre-test glibenclamide group. All groups received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, the animals received diazoxide vehicle or diazoxide (1.7, 5 and 15 µg/mouse, i.c.v.) in the presence of glibenclamide (3 µg/mouse, i.c.v.), 10 min before testing. Each value represents the median and quartile for 15 animals. $**P<0.01$ compared to pre-training morphine and pre-test glibenclamide.

3.2. Effect of K_{ATP} channel modulators and scopolamine on morphine state of memory

Fig. 3 indicates that glibenclamide injected 10 min before testing reversed the impairing effect of morphine (5 mg/kg,

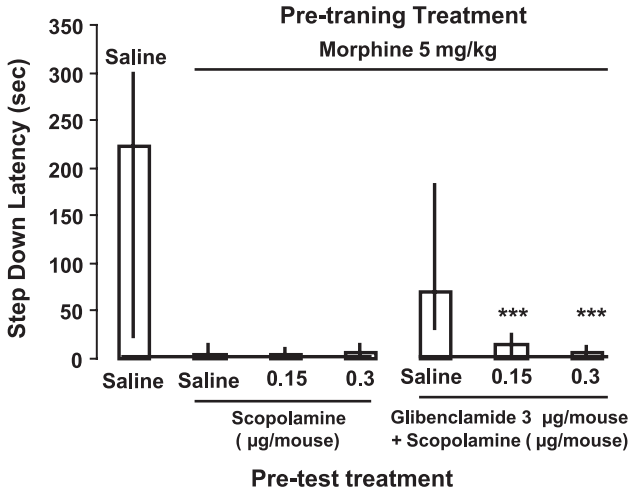

Fig. 6. The effect of pre-test administration of different doses of scopolamine on the step-down latencies compared to the pre-test glibenclamide group. All groups received morphine (5 mg/kg, s.c.) 30 min before training. On the test day, animals received saline or scopolamine (0.15 and 0.3 µg/mouse, i.c.v.) in the presence of glibenclamide (3 µg/mouse, i.c.v.), 10 min before testing. Each value represents the median and quartile for 15 animals. $***P<0.001$ compared to pre-training morphine and pre-test glibenclamide.

30 min before training) (H (3) = 33.03, $P < 0.001$). Moreover, the pre-test co-administration of glibenclamide and morphine increased morphine state dependence (H (3) = 15.56, $P < 0.01$).

Fig. 4 shows that diazoxide injected 10 min before testing did not reverse the memory impairing effect of morphine (5 mg/kg, 30 min before training) (H (3) = 3.99, $P = 0.26$). Pre-test co-administration of diazoxide and morphine decreased the morphine state dependence (H (3) = 28.27, $P < 0.001$)

Fig. 5 shows that diazoxide (1.7, 5 and 15 μg/mouse, i.c.v.) decreased the retrieval enhancing effect of glibenclamide (3 μg/mouse) (H (3) = 13.12, $P < 0.01$) in a dose-dependent manner.

Fig. 6 shows that scopolamine (0.15 and 0.3 μg/mouse) decreased the retrieval enhancing effect of glibenclamide (3 μg/mouse) (H (2) = 31.93, $P < 0.001$) in a dose-dependent manner.

4. Discussion

The passive avoidance test design used in the present study is suggested to be dependent upon opioid receptors of the amygdala (Gallagher and Kapp, 1978). The mechanisms of morphine-induced impairment of memory formation have not been fully elucidated, though μ-opioid receptor activation is essential (Izquierdo, 1979; Izquierdo and Dias, 1983a,b; Nishimura et al., 1990; Bruins Slot and Colpaert, 1999a). The previously reported observations that impairment of memory formation induced by acute pre-training morphine injection can be reversed by pre-test morphine in a time- and dose-specific manner are strongly suggestive of state-dependent learning (Bruins Slot and Colpaert, 1999a,b; Khavandgar et al., 2002). In the present study, the pre-test morphine administration exerted a facilitatory effect on retrieval in mice trained under morphine but not in animals trained under saline treatment (Fig. 1). This observation confirms the previous results. The response to morphine was reversed by naloxone, which again is in accordance with previous publications and suggests that the effect of morphine is exerted through the μ-opioid receptors (Shiigi et al., 1990). However, these investigators proposed that facilitation of memory retrieval by pre-test morphine administration might be due to the direct action of morphine rather than a state-dependent effect.

It has been shown that central K_{ATP} channel openers produce an antinociceptive effect similar to that of morphine (Narita et al., 1993). Moreover, the K_{ATP} channel blockers antagonize opioid analgesia (Ocana et al., 1990; Raffa and Martinez, 1995), suggesting the involvement of K_{ATP} channels in the analgesic effect of opioids. Stimulation of opioid receptors may also open potassium channels (Werz and MacDonald, 1983; North, 1989). Contrary to our expectation, the present study showed that the pre-test administration of the K_{ATP} channel blocker, glibenclamide, and not of diazoxide, restored the morphine-induced impairment of acquisition and showed retrieval. However, the pre-test administration of the K_{ATP} channel opener, diazoxide, did not retrieve the morphine-induced memory impairment but when used with morphine, the drug decreased morphine state dependence. The response induced by glibenclamide was antagonized by diazoxide pretreatment. This suggests the involvement of K_{ATP} channels in the memory retrieval but not interaction of K_{ATP} channel modulators with the action of morphine on the test day. One may conclude that the observed effect of glibenclamide in the present experiment was not exerted through the activation of μ-opioid receptors. In accordance with this hypothesis, other investigators have also reported that glibenclamide has no significant affinity for opioid receptors. Therefore, the possibility exists that blockade of K_{ATP} channels facilitates memory recall after pre-test administration of morphine by a mechanism which is not dependent on opioid receptors.

Introini and Baratti (1984) reported that the impairment of memory retention induced by post-training β-endorphin was reversed by physostigmine. Furthermore, it has been demonstrated that intraseptal morphine administration, at a dose that impairs performance of memory tasks, reduces acetylcholine output in the hippocampal formation, which suggests the involvement of the cholinergic system in some morphine actions (Ragozzino and Gold, 1994). On the other hand, Stefani and Gold (2001) have demonstrated that K_{ATP} channel modulators increase acetylcholine levels in the hippocampus, which is suggestive of the involvement of the cholinergic system in the effects of K_{ATP} channel modulators as well. In the present experiment the administration of scopolamine significantly prevented the effect of glibenclamide on memory retrieval on the test day.

In conclusion, the effect of glibenclamide on the test day, observed in the present experiments, is most likely exerted through an antagonistic effect on K_{ATP} channels and is less likely to be through its effects on the μ opioid receptors. The retrieval of memory on the test day by glibenclamide may be exerted through its effect on the cholinergic system.

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