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BETA1-ADRENORECEPTORS OF THE *CA1* AREA MEDIATE MORPHINE-MODIFIED STATE-DEPENDENT MEMORY IN RAT

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In our study, we investigated the effects of intra-*CA1* microinjections of a selective β1-adrenoreceptor antagonist, betaxolol, on state-dependent memory induced by morphine. A step-through passive avoidance task was used to assess memory retrieval. Male Wistar rats were bilaterally implanted with chronic cannulas in the *CA1* regions of the dorsal hippocampus by stereotaxic surgery seven days before training. Each animal was tested 24 h after training to measure the step-through latency and the time spent in a dark chamber of the apparatus. Post-training intra-*CA1* administrations of different doses of morphine (5 and 7.5 mg/kg, s.c.) decreased memory retrieval in the retention test (morphine-induced amnesia). The effect of post-training injections of 7.5 mg/kg morphine on retrieval was reversed by pre-test injection of the same dose of morphine. This phenomenon is named morphine state-dependent memory. The results also showed that pre-test intra-*CA1* microinjection of ineffective low doses of betaxolol (0.125 and 0.25 mg/rat) inhibited morphine-induced state-dependent memory retrieval. Taken together, our results suggest that the *CA1* may be potentially critical for morphine state-dependent memory, and the β1-adrenergic receptor mechanism(s) interact with the opioidergic system in the modulation of this type of memory in the *CA1*.

Keywords: morphine, hippocampus, *CA1*, memory, step-through task, betaxolol.

INTRODUCTION

State-dependent learning is a model for studying memory retrieval. This type of memory exists when experimental animals are in the same physiological state during both the acquisition and retrieval phases of memory [1]. State-dependent memory has been demonstrated using some drugs, such as morphine and other opioidergic agents [2, 3]. The measurement of the step-through latency in an inhibitory avoidance task has been used in pharmacological studies of memory in experimental animals. It is well known that the impairment effect of morphine is reversed by pretest administration of the same doses of morphine in an inhibitory avoidance model of memory [2, 4, 5].

We demonstrated earlier that post-training administration of morphine can impair retrieval in the inhibitory avoidance memory tests, and this is reversible by pre-test administration of morphine; the respective effect can be named morphine state-dependent memory retrieval [6, 7]. Morphine-induced amnesia [8] and morphine state-dependent memory [9] are antagonized by injections of naloxone; therefore, it seems that μ-opioid receptors mediate this effect of morphine on memory retrieval. It seems that these effects of morphine on memory processes may be due to interaction between central neurotransmitter systems in different regions of the brain, such as glutamatergic [10], cholinergic [11, 6], and noradrenergic [12].

Vast neuropharmacological studies clearly demonstrated a major role of norepinephrine in the regulation of cognitive functions; this is provided by interaction with two classes of adrenergic receptors, α and β. Although brain β-adrenergic receptors are substantially less numerous than α-receptors, they are crucial for memory formation. Noradrenergic neurons localized in the brainstem have widespread projections throughout different brain regions [13], including the neocortex and hippocampus [14, 15]. It was shown that microinjections of an adrenergic agent, such as norepinephrine, into the hippocampus potentiate memory formation [16].

Different studies using adrenergic agonists and antagonists demonstrated that central β-adrenergic receptors play an important role in memory formation [17-19]. Blocking of these receptors impairs different

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phases of the memory processes, namely acquisition [20, 21], consolidation [22, 23], retrieval [24, 25], and reconsolidation [18, 26]. All subtypes of β-adrenergic receptors (β1, β2, and β3) have been found in mammalian brain regions [27]. These receptors, by coupling to G proteins, activate adenylate cyclase and an intracellular cAMP-PKA-MAPK-CREB signaling pathway that is necessary for memory formation [28].

The hippocampus, a part of the medial temporal structures, plays a central and critical role in the formation of memory [29]. It is well known that β-adrenergic receptors in the *CA1* area, an important region of the hippocampus, are involved in the retrieval phase of several models of memory. Activation of β-adrenergic receptors in this area increases memory retrieval [28, 30]. Furthermore, β1-adrenergic [31, 32] and opioid [33] receptors are extensively expressed in the *CA1*. There are behavioral investigations indicating that opioidergic and adrenergic mechanisms are involved in memory formation [34, 35]. Based on these findings, we tried in our study to determine the possible involvement of β1-adrenergic receptors of the *CA1* area in morphine-modified state-dependent memory in rats using a step-through passive avoidance model.

METHODS

Animals, Surgery and Drug Administration. Adult male Wistar rats weighing 200-250 g at the time of surgery were used in this study. The animals were housed four per Plexiglas cage, with free access to water and food *ad libitum*, and kept at controlled temperature (23 ± 2°C) under a 12/12 h light-dark cycle (light beginning at 7:00 a.m.). All experiments were carried out during the light phase (between 9:00 and 14:00). Each experimental group consisted of seven animals. Procedures were performed in accordance with the National Academy Guide for the Care and Use of Animals in Research.

Seven days before the beginning of behavioral experiments, the animals were anesthesized by i.p. administration of ketamine hydrochloride (50 mg/kg) and xylazine (4 mg/kg) and cannulated using a stereotaxic instrument (Stoelting, USA). Two guide cannulas (22-gauge, 10 mm long) were positioned bilaterally 1 mm above the region of injection based on the stereotaxic coordinates of the *CA1* in the dorsal hippocampus, in accordance with the rat brain atlas (–3 mm anterior to the bregma, ±2 mm lateral to the sagittal suture, and 2.8 mm ventral from the surface of the skull) [36]. The cannulas were anchored to the skull with dental cement.

The drugs (morphine sulfate, Temad, Iran, and betaxolol, Sinadarou, Iran) were dissolved in sterile saline. Morphine was administrated subcutaneously (s.c.), while betaxolol was microinjected into the *CA1* by a Hamilton syringe and a needle (27-gauge, 14 mm long) joined together by a polyethylene tube. The latter solution was infused in a volume of 0.5 μl per side (1 μl/rat) within a period of 120 sec, to provide free diffusion of the drug in the injected region.

Behavioral Procedures. A step-through apparatus was used to evaluate inhibitory avoidance memory retrieval. This apparatus consisted of two (illuminated/dark) compartments (each 20×20×30 cm) connected via a small door (7×9 cm). The floor of the dark compartment was equipped with stainless steel rods (2.5 mm in diameter, with 10-mm intervals). Electrical AC shocks (50 Hz, 1 mA, 3 sec) could be delivered to these rods by an isolated stimulator.

Behavioral procedures included two phases, training and testing (with 1-day-long interval), as described in our pervious study [6].

On the training day, each rat was placed in the illuminated compartment; 10 sec later, the door was opened. Immediately after the animal entered the dark compartment, the door was closed, and the rat was transferred to the home cage. The latency of entering the dark compartment (step-through latency, STL) and the time spent in the latter (TSD) were measured. Animals with STLs longer than 100 sec were excluded from the research.

Each animal was placed again in the illuminated compartment 30 min later. Then the door was opened after 10 sec. As soon as the animal entered the dark compartment, and all four paws had been placed on the grid floor, the door was closed, and an electrical AC shock was immediately delivered to this chamber. The rat was temporarily transferred from the apparatus to its home cage about 20 sec after receiving the shock. Two min later, the rat again was placed in the light compartment (as in the prior trials). If the STL was longer than 120 sec, the acquisition stage of passive avoidance memory was successfully completed. This procedure was repeated for animals that had not completed the test successfully (each animal received electrical shocks not more than three times).

Long-term memory retrieval of animals was tested 24 h after training. The rats were placed in the illuminated chamber, and, after 10 sec, the door was

opened. Without using electrical shocks during this phase, the STLs and TSD were recorded for 300 sec for assessment of memory retrieval.

Experiments. Each animal received post-training administration of either saline or morphine s.c., as reported in our previous communication [6]. The rats also received pretesting intra-*CA1* microinjections of saline, or betaxolol + morphine, or saline s.c. All animal groups (each group included eight rats) were subjected to three experiments.

Experiment 1. The effects of post-training and pre-test injections of morphine on retrieval of inhibitory avoidance memory were evaluated in this experiment. Five animal groups (controls) received post-training administrations of saline (1 ml/kg, s.c.) or morphine (7.5 mg/kg, s.c.). On the test day, the rats received saline (1 ml/kg) or different doses of morphine (0.5, 2.5, 5.0, or 7.5 mg/kg, s.c.) 30 min before the test (pretest administrations), and memory retrieval was measured 30 min later (Fig. 1).

Experiment 2. The effects of pre-test intra-*CA1* microinjections of betaxolol on memory retrieval were investigated. Five groups of animals received post-training administrations of saline (1 ml/kg). On the test day, they received different pretest small intra-*CA1* doses of betaxolol (0.0, 0.0625, 0.125, 0.25, or 0.5 µg per rat) 30 min before retrieval testing (Fig. 2).

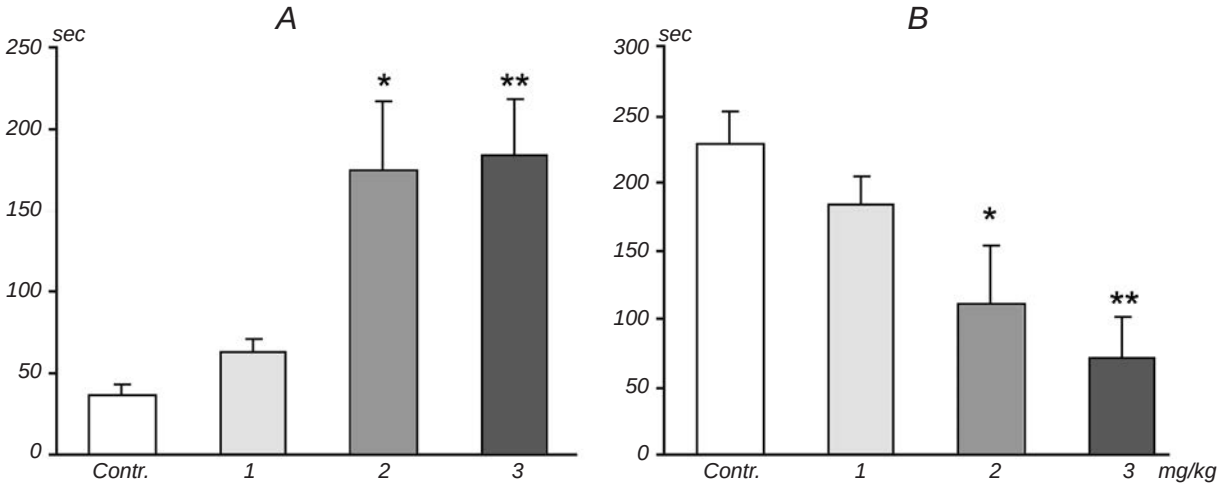
Experiment 3. The effects of pre-test intra-*CA1* microinjections of betaxolol on morphine-modified state-dependent memory were investigated in experiment 3. Four groups of animals were used in this experiment. All groups of rats received post-training administrations of morphine (7.5 mg/kg, s.c.). Then, these groups received intra-*CA1* microinjections of different doses of betaxolol (0.0, 0.0625, 0.125, or 0.25 µg per rat) plus morphine (7.5 mg/kg) 30 min before testing on the test day (Fig. 3). It is important to note that the interval between two injections was 5 min long.

After behavioral testing, animals were euthanized and microinjected with 1% methylene blue into the *CA1* (0.5 µl per side). Then they were decapitated; their brains were removed and placed in 10% formalin solution. After 10 days, the brains were sliced, and the sites of injections were verified according to the rat brain atlas [36]. Data from rats that received drugs outside the *CA1* were omitted.

Data Analysis. The data are expressed as means ± ± s.e.m. Statistical processing was performed using one-way analysis of variance (ANOVA). *Post-hoc* comparison of the means was carried out with the Tukey's test for multiple comparisons when appropriate. Intergroup differences were considered significant at $P < 0.05$. Calculations were performed using SPSS statistical software.

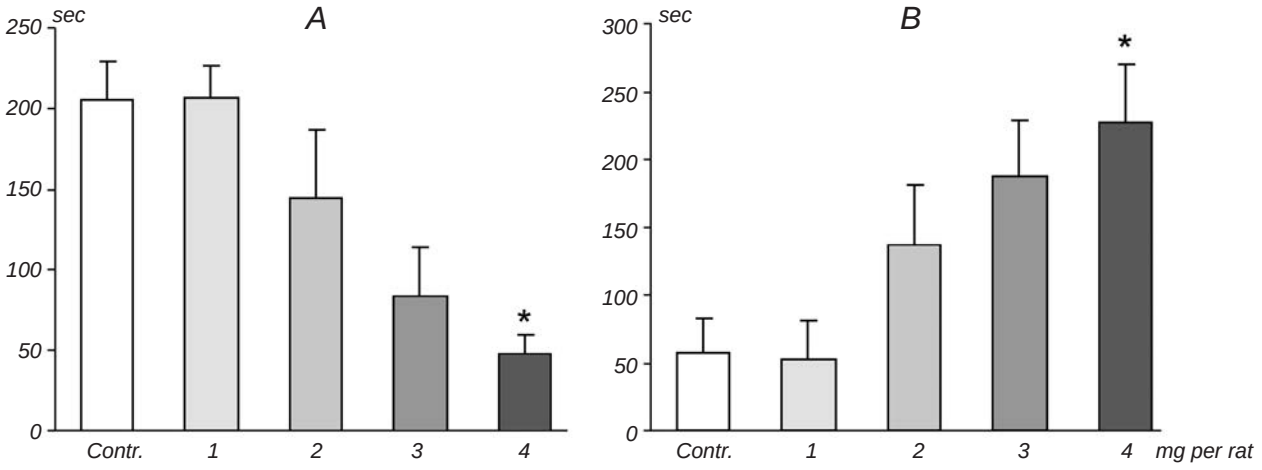
RESULTS

Effect of Morphine on Memory Retrieval. Figure 1 shows the effects of morphine (post-training/pre-testing administrations) on the STLs (Fig. 1A) and



F i g. 1. Effect of morphine on memory retrieval. Vertical scale: in A, step-through latencies, sec; in B, time spent in the dark chamber, sec. The animals received post-training morphine (7.5 mg/kg, s.c.) and also pre-testing saline (1 ml/kg s.c., Contr.) or morphine (2.5, 5.0, and 7.5 mg/kg, s.c., 1-3, respectively). The columns show means ± s.e.m. ($n = 8$). *$P < 0.05$, and **$P < 0.01$, compared to the control group (Contr., morphine, 7.5 mg/kg, s.c., and saline, 1.0 ml/kg, s.c.).

Р и с. 1. Вплив морфіну на збереження пам'ятних слідів.

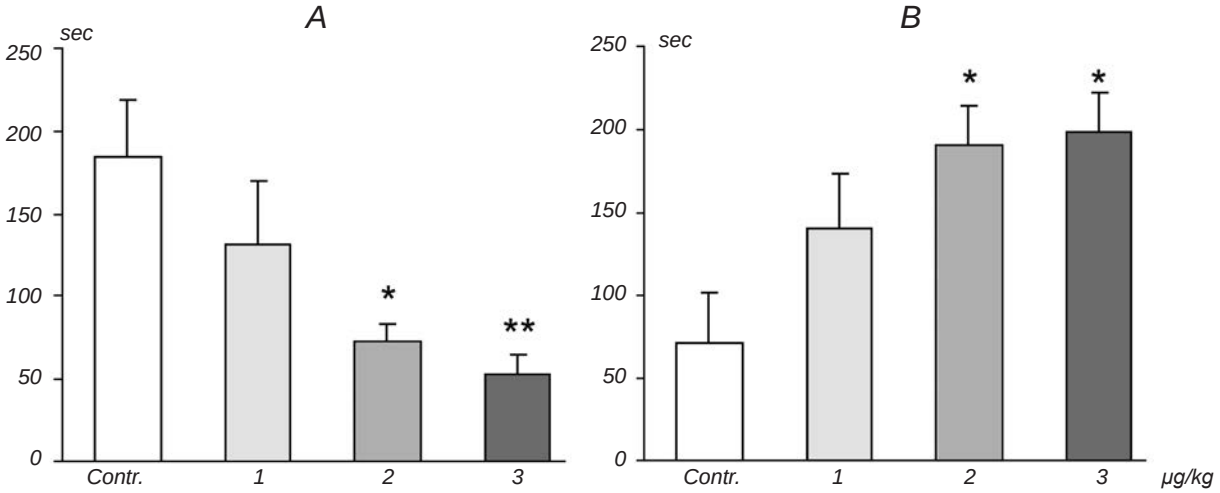


F i g. 2. Effect of betaxolol on memory retrieval. All animals received post-training saline (1.0 ml/kg, s.c.) and also pre-testing saline (1.0 μl per rat) or betaxolol (0.0625, 0.125, 0.25, and 0.5 μg per rat, 1-4, respectively). The columns show means ± s.e.m. ($n = 8$). *$P < 0.05$, compared to the control saline group (Contr.). Other designations are the same as in Fig. 1.

Р и с. 2. Вплив бетаксололу на збереження пам'ятних слідів.

total TSD (B). Statistical analysis by one-way ANOVA showed that, in animals with impaired retrieval due to post-training administration of morphine (7.5 mg/kg), pre-test administration of morphine (2.5, 5.0, and 7.5 mg/kg, s.c.) restored the retrieval. The effect of morphine was manifested in the increased STLs [F (3, 28) = 7.033, $P = 0.0011$] and decreased TSD [F (3, 28) = 5.48, $P < 0.0043$], as compared with the control values. This phenomenon is well known as morphine-induced (morphine-modified) state-dependent memory retrieval. The maximum restoration was observed with the maximum used dose of morphine (7.5 mg/kg; $P < 0.01$).

Effect of Intra-*CA1* Microinjection of Betaxolol on Memory Retrieval. Figure 2 shows the effects of pre-test microinjections of betaxolol on the STLs (Fig. 2A) and total TSD (B). Statistical analysis by one-way ANOVA showed that betaxolol (0.0625, 0.125, 0.25, and 0.5 μg per rat) decreased the STLs [F (4, 35) = 4.99, $P = 0.0047$] in a dose-dependent manner and increased the TSD [F(4, 35) = 4.033, $P = 0.0098$)], as compared with the control values.



F i g. 3. Effect of betaxolol on memory retrieval. All animals received post-training morphine (7.5 mg/kg, s.c.) and also pre-testing low doses of betaxolol (0.0625, 0.125, and 0.25 μg per rat, 1-3, respectively) plus morphine (7.5 mg/kg, s.c.). The columns show means ± s.e.m. ($n = 8$). *$P < 0.05$ and ** $P < 0.01$, compared to the control group (Contr., saline/betaxolol).

Р и с. 3. Вплив бетаксололу на збереження пам'ятних слідів, модифіковане під дією морфіну.

These observations are indicative of memory retrieval impairment. The Tukey's test showed that the maximum modification was obtained with 0.5 μg betaxolol per rat ($P < 0.01$).

Effect of Pretest Intra-*CA1* Microinjection of Betaxolol in the Presence of Morphine on Memory Retrieval. Figure 3 shows the effect of pre-test intra-*CA1* administration of betaxolol on morphine-modified state-dependent memory retrieval. One-way ANOVA indicated that animals that received post-training and pre-test administrations of morphine (7.5 mg/kg) and pre-test intra-*CA1* administrations of low doses of betaxolol (0.0625, 0.125, and 0.25 μg per rat) demonstrated dose-dependent decreases in the STLs [$F(3, 28) = 4.79$, $P = 0.0081$, Fig. 1A] and increases in the TSD [$F(3, 28) = 4.189$, $P = 0.0156$, B).

DISCUSSION

In our study, the role of β1-adrenergic receptors of *CA1* of the dorsal hippocampus in morphine-modified state-dependent memory has been evaluated by using the step-through passive avoidance model. According to our own results, which are in agreement with previous reports [3, 9], post-training systemic morphine administration dose-dependently decreased retrieval in the passive avoidance task on the test day and, thus, induced amnesia. Furthermore, the memory retrieval impairment induced by post-training administration of morphine was reversed by pre-test morphine administration, also dose-dependently. These data, in agreement with other previous studies, indicate that morphine effectively modifies state-dependent memory [37, 38]. Considering that injection of naloxone decreases the effect of morphine on memory [39], it seems that μ-opioid receptors mediate this phenomenon. Although several studies indicated that different central neurotransmitter systems are involved in the effect of morphine on memory retrieval, precisely the participation of the hippocampus is important for this effect.

Our experiments also showed that the pre-test microinjection of betaxolol, a selective antagonist of β1-adrenergic receptor, into the *CA1* dose-dependently reduces memory retrieval. These data are in agreement with previous communications. Studies using adrenergic agents indicated that adrenergic receptors play a rather important role in the memory processes. The enhancement of memory retrieval due to peripherally and centrally administered adrenoreceptor agonists can be suppressed by different antagonists of these receptors. Propranolol and timolol (i.e., β-adrenergic receptor antagonists) have been shown to decrease the level of acquisition of various models of memory in rats. On the other hand, β-adrenergic agonists, including isoprenaline and clenbuterol, increased retrieval of memory retention [12, 17, 18, 40].

It seems that activation of β-adrenergic receptors by isoproterenol (an agonist) increases calcium currents and facilitates synaptic transmission, i.e., phenomena needed for the memory processes. In addition, activation of β-adrenergic receptors up-regulate cAMP-linked intracellular signaling pathways [41-43] maintaining synaptic transmission.

In the basolateral nuclei of the amygdala, synaptic facilitation is mediated by activation of both β1- and β2-adrenergic receptors [43]. The basolateral amygdala modulates memory formation via activation of these subtypes of β-adrenoreceptors [43-45]. Although it was reported that pre-test intra-amygdalar microinjections of low doses of a β1-adrenergic receptor antagonist, atenolol, did not alter retrieval in the passive avoidance memory test [46], other studies showed that the blockade of β1-receptors in the basolateral amygdala impaired auditory fear memory [47]. Xamoterol, a β1-adrenergic receptor agonist, effectively increased the retrieval in the contextual fear memory test. This response was reversed by betaxolol administrations [48].

Our results revealed that blocking of β1-adrenergic receptors in the *CA1* by pre-test intra-*CA1* microinjections of ineffective low doses of betaxolol (which did not affect memory retrieval *per se*) disrupted retrieval in the morphine state-dependent memory tests. Some studies showed that noradrenergic receptors are involved in state-dependent memory [49, 50]. For example, it was shown that the dorsal hippocampal α-adrenergic system modulates retrieval in scopolamine-modulated state-dependent memory [51]. It was also reported that drug-related memories can be attenuated by injections of propranolol [52]. Interactions between β-adrenergic receptors and opioidergic systems in behavioral tests, including such effects as corticosterone release in morphine-dependent rats [53], morphine-conditioned place preference memory retrieval in mice [54], and memory consolidation and opiate withdrawal [55], were reported in a number of publications. On the other hand, β-adrenergic receptor activation has been known to play an important role in memory-

related processes in the hippocampus [28, 30]. The blockade of β-adrenergic receptors in the *CA1* area of the hippocampus impairs memory formation by attenuating the activity of the cAMP-PKA-CREB intracellular pathway [56].

In conclusion, our observations support the statement that the *CA1* region of the dorsal hippocampus is a target area for morphine-modified state-dependent memory. It seems that the role of the *CA1* in mediating this effect of morphine may be partly due to activation of β1-adrenergic receptors in this area. The blockade of *CA1* β1-adrenergic receptors prevents morphine-induced modulation of state-dependent memory. The involvement of these receptors in this effect of morphine may be mediated, directly or indirectly, via other neurotransmitter-related mechanisms, such as acetylcholinergic, glutamatergic, and dopaminergic ones.

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МОДИФІКАЦІЯ МОРФІНОМ ПАМ'ЯТІ, ЗАЛЕЖНОЇ ВІД СТАНУ, У ЩУРІВ: УЧАСТЬ β1-АДРЕНОРЕЦЕПТОРІВ ДІЛЯНКИ *CA1*

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Р е з ю м е

У нашій роботі ми досліджували впливи мікроін'єкцій селективного антагоніста β1-адренорецепторів бетаксололу в ділянку *CA1* гіпокампа на формування залежної від стану пам'яті, індукованої ін'єкціями морфіну. Для оцінки ефективності здобування пам'ятних слідів використовували тест пасивного уникання. Самцям щурів лінії Вістар стереотаксично імплантували канюлі в ділянку *CA1* дорсального гіпокампа за сім днів до тренування. Кожну тварину тестували через 24 год після тренування з вимірюванням латентного періоду уникання та тривалості перебування у темному відсіку тест-установки. Підшкірне введення 5 або 7.5 мг/кг морфіну після тренування послаблювало збереження пам'ятних слідів у відповідному тесті (індукована морфіном амнезія). Ефекти ін'єкцій 7.5 мг/кг морфіну після тренувань спотворювалися внаслідок ін'єкцій морфіну в тій самій дозі, виконаних перед тестом. Цей феномен кваліфікується як модифікація залежної від стану пам'яті під впливом морфіну. Як показали результати наших дослідів, мікроін'єкції в ділянку *CA1* малих (неефективних) кількостей бетаксололу (0.125 або 0.25 мкг на тварину) послаблювали збереження індукованих морфіном модифікацій залежної від стану пам'яті. У цілому наші результати дозволяють вважати, що ділянка *CA1* є критичною для формування модифікованої морфіном залежної від стану пам'яті і що β1-адренергічні рецепторні механізми взаємодіють із опіоїдергічною системою в перебігу модуляції пам'яті цього типу у щурів.

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