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Role of nitric oxide in the rat hippocampal CA1 area on morphine-induced conditioned place preference

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Abstract

Effects of intrahippocampal CA1 injections of L-arginine, a nitric oxide (NO) precursor, and N^G-nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase inhibitor, on morphine-induced conditioned place preference in male Wistar rats were investigated. Animals received subcutaneous (s.c.) injections of saline (1.0 ml/kg) or morphine (0.5–7.5 mg/kg) once daily for 3 days to induce conditioned place preference. The administration of L-arginine (0.3, 1.0, and 3.0 μg/rat), but not L-NAME (0.3, 1.0, and 3.0, μg/rat), prior to administration of morphine (5.0 mg/kg) during acquisition of morphine-induced conditioned place preference increased morphine-induced conditioned place preference, but the interaction between the response to morphine and/or L-arginine was not statistically significant. The response to L-arginine was blocked by L-NAME pre-administration. L-Arginine or L-NAME by itself did not induce conditioned place preference. The administration of L-arginine but not L-NAME, 1 min before conditioned place preference testing, increased the expression of morphine-induced conditioned place preference. Pre-administration of L-NAME blocked the L-arginine response. It is concluded that NO in the rat hippocampal CA1 area may be involved in morphine-induced conditioned place preference.

Keywords: Morphine; Conditioned place preference; Hippocampus; CA1; Nitric oxide (NO); L-Arginine; L-NAME (N^G-nitro-L-arginine methyl ester); (Rat)

1. Introduction

Nitric oxide (NO), which participates in a variety of physiological functions, is an endogenously and enzymatically generated molecule of great pharmacological interest and physiological importance (Fukuto and Mayer, 1996). As a neurotransmitter, NO plays a role in the regulation of behavior (Moncada et al., 1991). NO has been implicated in the actions of opioids (Kivastik et al., 1996). Thus, NO is thought to play a role in the expression (Dambisya and Lee, 1996) and development (Majeed et al., 1994; Machelska et al., 1997; Lue et al., 1999) of morphine tolerance and dependence in laboratory animals. The involvement of excitatory neurotransmitters in opioid withdrawal, a sign of drug-dependent phenomena (Rasmussen et al., 1991; Vaupel et al., 1997), has been suggested. The finding that NO is produced postsynaptically in response to activation of central excitatory amino acids (Garthwaite, 1991) raises the possibility that suppression of the signs of withdrawal by *N*-methyl-D-aspartate (NMDA) receptor antagonists may be linked to inhibition of NO synthesis (Dambisya and Lee, 1996). It has been shown that antagonists acting at NMDA-type glutamate receptors block both the development and the expression of opioid dependence in laboratory animals (Trujillo and Akil, 1991; Herman et al., 1995).

The reinforcing effects of opiates have long been known and indicate that the brain mesolimbic dopaminergic system is involved in these reinforcement effects (Carr and White, 1983, 1986; Wise, 1987). Bardo (1998) postulated that, in addition to the mesolimbic dopamine system, other structures including the hippocampus might play a role in reward. It was shown that the dorsal hippocampus contains the highest concentration of hippocampal dopamine (Ishikawa et al., 1982). A lot of evidence suggests that NO may be involved in mediating the release of dopamine (Zhu and Luo, 1992; Lonart et al., 1993; Segieth et al., 1996). Several

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findings also demonstrate that NO mediates cocaine-induced dopaminergic behaviors such as reverse tolerance and conditioned place preference (Kim and Park, 1995; Itzhak et al., 1998). Further evidence indicates that NO plays a role in the modulation of dopaminergic effects elicited by morphine (Calignano et al., 1993).

The present research was designed to investigate the possible involvement of the NO system in the rat hippocampus CA1 area on morphine-induced conditioned place preference.

2. Materials and methods

2.1. Subjects

Subjects were male Wistar rats (Pasteur Institute of Iran, Tehran, Iran) weighing between 200 and 220 g at the start of the experiments. Animals were housed four per cage in a controlled colony room (temperature 22±3 °C). They were maintained on a 12-h light/dark cycle (07:00–19:00 h) with food and water ad libitum. They were housed in the colony for at least 1 week prior to commencement of experiments. Testing was conducted during the light phase. Each animal was tested once. Eight animals were used in each experiment. The protocol has been approved by the ethics committee of the faculty of science of Tehran University (357; Nov. 8, 2000).

2.2. Drugs

The drugs used in the present study were morphine sulfate (Temad, Tehran, Iran), L-arginine (Sigma, USA), N^G-nitro-L-arginine methyl ester (L-NAME; Research Biochemical, USA), and sodium pentobarbital (Sigma). These drugs were prepared freshly in sterile 0.9% NaCl solution. Morphine and pentobarbital were injected subcutaneously (s.c.) and intraperitoneally (the volume of morphine and pentobarbital injections was 1.0 ml/kg), respectively. L-Arginine and L-NAME were bilaterally injected into the hippocampal CA1 area (the volume of the drug injections was 1.0 μl/rat). Vehicle injections were of the appropriate volume of 0.9% physiological saline.

2.3. Surgery

The animals were anesthetized with sodium pentobarbital (42–45 mg/kg) and placed in a stereotaxic apparatus, with the incisor bar set at approximately 3.0 mm below horizontal zero to achieve a flat skull position. An incision was made to expose the rat skull. Two holes were drilled in the skull, as described in previous studies (Ishikawa et al., 1982; Packard and White, 1991), at stereotaxic coordinates from AP −3.0 to −3.8 mm posterior to bregma, and from L±1.8 to ±2.2 mm according to the atlas of Paxinos and Watson (1987). Two guide cannulae (21 gauge) were inserted into the holes. For animals receiving bilateral injections into the CA1 area of the hippocampus, the guide cannulae were lowered 2.5 mm below bregma through the holes drilled at the above-mentioned coordinates. The guide cannulae were anchored with a jeweler's screw, and the incision was closed with dental cement. After surgery, dummy inner cannulae that extended 0.5 mm beyond the guide cannulae were inserted into the guide cannulae and left in the place until injections were made. All animals were allowed to recover for 1 week before behavioral testing began.

2.4. Intrahippocampal injection

The animals were gently restrained by hand; the dummy cannulae were removed from the guide cannulae. For intrahippocampal injections of drugs, a 5.0-μl glass Hamilton syringe was used. The injection (inner) cannulae (27 gauge), which projected a further 0.5 mm ventral to the tip of the guides, were attached with polyethylene tubing (0.6-mm internal diameter) to the Hamilton syringe. The injection volume was 1.0 μl for all groups. Injections were made over a 30-s period, and the injection cannulae were left in the guide cannulae for an additional 60 s to facilitate the diffusion of the drugs.

2.5. Histological verification

After completion of behavioral testing, animals were killed with an overdose of chloroform. Ink (0.5 μl of 1% aquatic methylene blue solution) was injected into the guide cannulae, using 27-gauge injection cannulae that projected a further 0.5 mm ventral to the tip of the guides, to aid in histological verification. Brains were removed and fixed in a 10% formalin solution for 10 days before sectioning. Sections were taken through the brain areas of cannula placements, and the cannula placements were verified using the atlas of Paxinos and Watson (1987). Data from rats with injection sites located outside the hippocampal CA1 area were not used in the analyses.

2.6. Apparatus

A two-compartment conditioned place preference apparatus (30×60×30 cm) was used in these experiments. Place conditioning was conducted using an unbiased procedure, with minor changes to the design previously described (Shippenberg et al., 1996). The apparatus was made of wood. Both compartments were identical in size (the apparatus was divided into two equal-sized compartments by means of a removable white wall) and shading (both were white), but distinguished by texture and olfactory cue. To provide the tactile difference between the compartments, one of the compartments had a smooth floor, and the other compartment had a nylon white mesh floor. A drop of vinegar was placed at the right corner of the compartment textured with

nylon mesh floor to provide the olfactory cue difference between the compartments. The two compartments also had different black stripes (on three of their sides). In this apparatus, rats show no consistent preference for either compartment.

2.7. Procedure

2.7.1. Familiarization or habituation

On day 1, the animals were adapted to the conditioned place preference apparatus for 15 min. The removable wall was raised, thereby allowing each rat to move freely between the two compartments. They were then randomly assigned to one of two groups (four rats per group) for place conditioning.

2.7.2. Conditioning or induction phase

This phase consisted of six, 45-min sessions (three saline and three drug pairing). These sessions were conducted twice each day (day 2, 3, and 4) with a 6-h interval. During these sessions, the removable wall was inserted along the seam separating the two compartments, and each group of rats was then confined to one compartment. The animals of each group were injected with morphine and they were immediately confined to one compartment of the apparatus for 45 min. Following administration of saline, they were confined to the other compartment for 45 min. Treatment compartment and order of presentation of morphine and saline were counterbalanced. Conditioning was conducted as previously described using an unbiased procedure (Shippenberg et al., 1996).

2.7.3. Testing phase

Test sessions were carried out on day 5, 1 day after the last conditioning session, in a morphine-free state. Each animal was tested only once. For test sessions, the removable wall was raised and each uninjected animal (with morphine) was allowed free access to both compartments of the apparatus for 15 min. An observer then assessed the time spent in the morphine- and saline-paired environments. The location of the animal was determined by the position of the front paws. The scores (conditioning scores in s) represent the time spent in the drug-paired compartment minus the time spent in the saline-paired environment, and are expressed as means±S.E.M.

2.8. Induction and assessment of place conditioning by morphine

In a pilot study, the effects of different doses (0.5, 1.25, 2.5, 5.0, and 7.5 mg/kg) of morphine subcutaneously injected on the induction of conditioned place preference were determined. Morphine or saline was injected once daily for 3 days as described in detail elsewhere (Shippenberg et al., 1996). Conditioned place preference induction was assessed by determining the time spent in the morphine- and saline-paired compartments of the conditioned place preference apparatus during a 15-min period for each drug dose within groups in a morphine-free state, and calculated as the conditioning scores and expressed as means±S.E.M. To examine state-dependent learning (as mentioned by Overton, 1973), morphine was administered prior to testing. It was found that the size of the conditioned place preference response was not altered. Therefore, the animals were tested in a morphine-free state. This eliminates the possibility that morphine-induced motor effects influence responding (Olmstead and Franklin, 1997b).

2.9. Measurement of the effects of L-arginine (NO precursor) and L-NAME (NO synthase inhibitor) on the acquisition and expression of conditioned place preference induced by morphine

Effects of intrahippocampal CA1 injection of different doses of L-arginine or L-NAME on the acquisition of the conditioned place preference induced by morphine were determined as follows. Rats received morphine (5.0 mg/kg) or vehicle (s.c.) once daily in a 3-day schedule of conditioning. L-Arginine (0.3, 1.0, and 3.0 μg/rat) or L-NAME (0.3, 1.0, and 3.0 μg/rat) was injected once a day during the conditioning period 1 min before the administration of morphine (three sessions); the conditioning scores then were measured in a drug-free state (testing day). The same above-mentioned doses of both L-arginine and L-NAME were injected once (testing day) in a morphine-free state. The conditioning scores were measured 1 min after drug injection to evaluate their effects on the expression of the conditioned place preference induced by morphine.

2.10. Statistical analysis

The two-way analysis of variance (ANOVA) or, when appropriate, the one-way ANOVA followed by the Tukey–Kramer or Newman–Keul's multiple comparison tests were used to determine the effects of the various treatments on morphine-induced place conditioning. P values less than 0.05 were considered as significant.

3. Results

3.1. Dose–response curve for place preference conditioning induced by morphine in opioid-naive rats

Fig. 1 shows the effect of morphine on place preference conditioning in rats. Animals that received saline (1.0 ml/kg) during the conditioning sessions exhibited no preference for either of the place cues. The mean time spent in the smooth floor compartment minus that spent in the textured one was 31 s, twice per day—six sessions. Administration

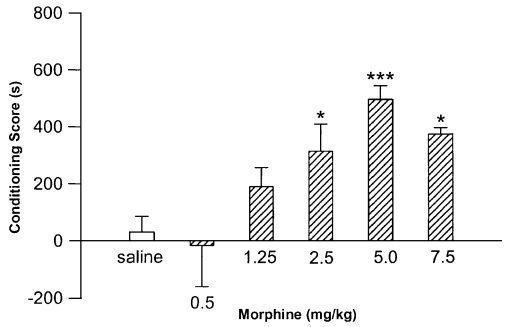

Fig. 1. Effect of morphine on conditioned place preference induction in opioid-naive rats. Animals received saline (1.0 ml/kg, s.c.) or morphine (0.5, 1.25, 2.5, 5.0, and 7.5 mg/kg, s.c.), once daily for 3 days. Control group received saline (1.0 ml/kg, s.c.), twice daily for 3 days. The values are expressed as mean conditioning scores±S.E.M. Conditioning score is defined as the time spent in the drug-paired place minus that spent in the saline-paired place. *P<0.05, ***P<0.001 different from the saline control group.

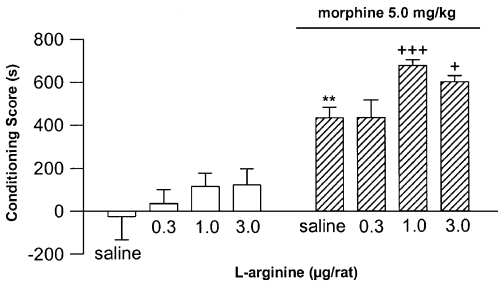

Fig. 2. Effect of morphine and/or L-arginine on the acquisition of conditioned place preference in opioid-naive rats. Animals received saline (1.0 µl/rat, intrahippocampal) or L-arginine (0.3, 1.0, and 3.0 µg/rat, intrahippocampal) in the presence or absence of morphine (5.0 mg/kg, s.c.) injection, once daily for 3 days. The values are expressed as mean conditioning scores±S.E.M. Conditioning score is defined as the time spent in the drug-paired place minus that spent in the saline-paired place. **P<0.01 different from saline control group. +P<0.05, +++P<0.001 different from the respective morphine control group.

of morphine (0.5, 1.25, 2.5, 5.0, and 7.5 mg/kg) during the conditioning sessions induced conditioned place preference [one-way ANOVA; $F(5,42)=5.9$, $P<0.001$]. Morphine 0.5 and 1.25 mg/kg failed to produce significant conditioning in animals and no preference for either of the place cues was seen. The maximum response was observed with 5.0 mg/kg of the opioid. In view of the results, morphine 5.0 mg/kg conditioning sessions were used for subsequent studies.

3.2. Effect of nitric oxide synthesis precursor and inhibitor on the acquisition of morphine-induced conditioned place preference in opioid-naive rats

L-Arginine, a precursor of nitric oxide (NO) synthesis, and L-NAME, an inhibitor of NO synthase, were used in combination with morphine during acquisition of conditioned place preference (as described in Materials and methods).

Fig. 2 shows the effect of L-arginine on morphine-induced conditioned place preference. The results indicate that morphine but not L-arginine induced conditioned place preference. The combination of morphine (5.0 mg/kg) with different doses of L-arginine (0.3, 1.0, and 3.0 µg/rat), during acquisition of conditioned place preference, elicited the enhancement of conditioned place preference. However, two-way ANOVA indicated no significant interaction between the responses to morphine and/or L-arginine [factor morphine, $F(1,56)=110.8$, $P<0.0001$; factor L-arginine, $F(3,56)=3.4$, $P<0.05$; factor morphine×L-arginine, $F(3,56)=0.2$, $P>0.05$].

Fig. 3 shows the effect of the NOS inhibitor, L-NAME, on morphine-induced conditioned place preference. There was no significant interaction between the responses to morphine (5.0 mg/kg) and/or L-NAME (0.3, 1.0, and 3.0 µg/rat) [two-way ANOVA; factor morphine, $F(1,56)=70.9$, $P<0.0001$; factor L-NAME, $F(3,56)=1.5$, $P>0.05$; factor morphine×L-NAME, $F(3,56)=0.2$, $P>0.05$].

Fig. 4 shows the effect of L-NAME on the response induced by the combination of morphine and L-arginine. One-way ANOVA showed that L-NAME blocked the response induced by the combination of morphine with L-arginine [$F(4,35)=8.5$, $P<0.0001$].

3.3. Effect of nitric oxide synthesis precursor and inhibitor on the expression of morphine-induced conditioned place preference in morphine-administered rats

Fig. 5 shows the effect of L-arginine or L-NAME on the expression of morphine-induced conditioned place preference. The drugs were administered 1 min before conditioned place preference testing (as described in Materials and methods). One-way ANOVA showed a significant difference between the response to morphine and that induced by morphine plus L-arginine (0.3, 1.0, and 3.0 µg/rat) or L-

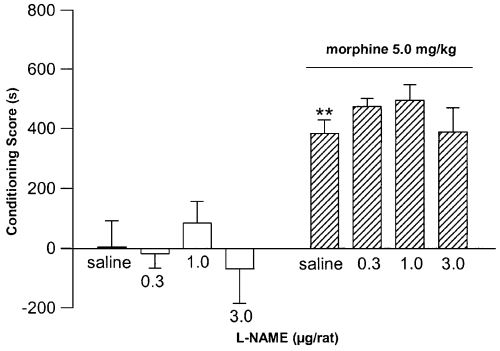

Fig. 3. Effect of morphine and/or L-NAME on the acquisition of conditioned place preference in opioid-naive rats. The animals received saline (1.0 µl/rat, intrahippocampal) or L-NAME (0.3, 1.0, and 3.0 µg/rat, intrahippocampal) in the presence or absence of morphine (5.0 mg/kg, s.c.) injection, once daily for 3 days. The values are expressed as mean conditioning scores±S.E.M. Conditioning score is defined as the time spent in the drug-paired place minus that spent in the saline-paired place. **P<0.01 different from the saline control group.

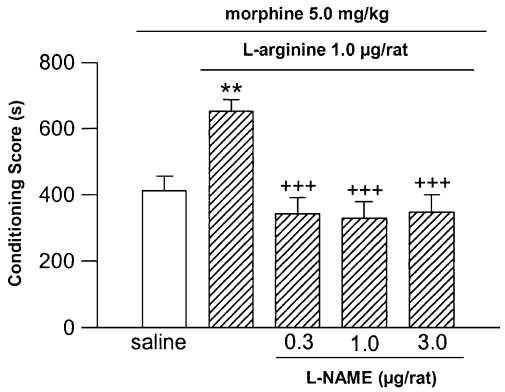

Fig. 4. Effect of L-NAME on the place preference conditioning induced by morphine in combination with L-arginine. The animals received L-arginine (1.0 μg/rat, intrahippocampal) or L-arginine plus L-NAME (0.3, 1.0, and 3.0 μg/rat, intrahippocampal) 1 min before morphine (5.0 mg/kg, s.c.) injection, once daily for 3 days. Saline control group received saline (1.0 μl/rat, intrahippocampal) 1 min before morphine (5.0 mg/kg, s.c.) injection, once daily for 3 days. The values are expressed as mean conditioning scores±S.E.M. Conditioning score is defined as the time spent in the drug-paired place minus that spent in the saline-paired place. $^{**}P<0.01$ different from the saline control group. $+++P<0.001$ different from the L-arginine control group.

NAME (0.3, 1.0, and 3.0 μg/rat) [$F(6,49)=4.2$, $P<0.01$]. Post hoc analysis showed that L-arginine but not L-NAME increased the expression of morphine-induced conditioned place preference.

Fig. 6 shows the effect of L-arginine with or without L-NAME on the expression of morphine-induced conditioned place preference. One-way ANOVA indicated a significant difference between the response to L-arginine with or without L-NAME on the expression of morphine-induced conditioned place preference [$F(4,35)=10.4$, $P<0.0001$].

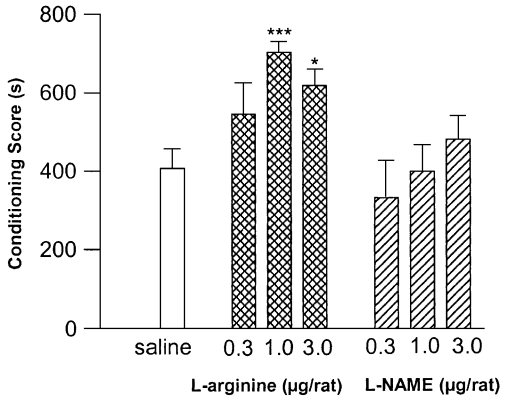

Fig. 5. Effect of L-arginine or L-NAME on the expression of morphine-induced conditioned place preference. The animals received morphine (5.0 mg/kg, s.c.) or saline (1.0 ml/kg, s.c.) in a 3-day schedule of conditioning (as mentioned in Materials and methods). On the day of test, animals received saline (1.0 μl/rat, intrahippocampal), L-arginine (0.3, 1.0, and 3.0 μg/rat, intrahippocampal), or L-NAME (0.3, 1.0, and 3.0 μg/rat, intrahippocampal) 1 min before testing. The values are expressed as mean conditioning scores ±S.E.M. Conditioning score is defined as the time spent in the drug-paired place minus that spent in the saline-paired place. $^{*}P<0.05$, $^{***}P<0.001$ different from the saline control group.

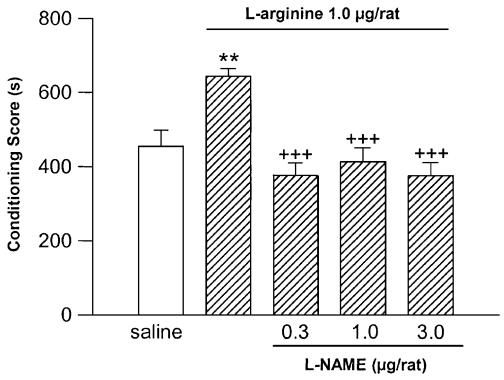

Fig. 6. Effect of L-arginine with or without L-NAME on the expression of conditioned place preference induced by morphine. The animals received morphine (5.0 mg/kg, s.c.) or saline (1.0 ml/kg, s.c.) in a 3-day schedule of conditioning (as mentioned in Materials and methods). On the day of test, animals received saline (1.0 μl/rat, intrahippocampal), L-arginine (1.0 μg/rat, intrahippocampal) or L-arginine plus L-NAME (0.3, 1.0, and 3.0 μg/rat, intrahippocampal) 1 min before testing. The values are expressed as mean conditioning scores ±S.E.M. Conditioning score is defined as the time spent in the drug-paired place minus that spent in the saline-paired place. $^{**}P<0.01$ different from the saline control group. $+++P<0.001$ different from the L-arginine control group.

Further analysis indicated that L-NAME blocked the enhancing effect of L-arginine on the expression of morphine-induced conditioned place preference.

4. Discussion

The hippocampal formation is now believed to be an essential component of the learning and memory systems of the brain (Sutherland and McDonald, 1990; Packard and White, 1991; Squire, 1992; LeDoux, 1993; Wan et al., 1994; Shen et al., 1996). Nitric oxide (NO) is linked with memory formation, called long-term potentiation, which occurs in the hippocampus after a neuron or group of neurons receive several simultaneous signals (Schuman and Madison, 1991; Holscher and Rose, 1992). Moreover, the hippocampus may be involved in conditioned place preference (McBride et al., 1999; Lu et al., 2000; Ferbinteanu and McDonald, 2001). In the present study, the effects of intrahippocampal injection of a precursor of NO (L-arginine) and an inhibitor of NO synthesis (L-NAME) on the acquisition and expression of morphine-induced conditioned place preference were investigated.

Rats were administered by morphine (5.0 mg/kg, three sessions) subcutaneously (s.c.) using an unbiased conditioned place preference paradigm. They showed a significant conditioned place preference. The animals were tested for conditioned place preference in a morphine-free state. The results are in agreement with others in this respect (Shippenberg et al., 1996). Although it has been shown that chronic treatment with L-arginine attenuates morphine antinociception by increasing brain NO synthase (NOS) activity and by decreasing the concentration of morphine in brain

areas including the hippocampus (Bhargava and Bian, 1997; Bhargava et al., 1997), our results show that the NO precursor, L-arginine, when administered into the hippocampal CA1 area during conditioning did not induce conditioned place preference, but increased the morphine-induced conditioned place preference without there being a statistically significant interaction between the responses to morphine and/or L-arginine. Since the response to morphine was increased rather decreased in the present study, L-arginine does not influence the concentration of morphine. Effect of L-arginine plus morphine was blocked by L-NAME pre-administration. L-NAME, which is an inhibitor of NO formation by competing with L-arginine for NOS (Bozarth et al., 1993), when injected during acquisition neither induced conditioned place preference by itself nor altered morphine-induced conditioned place preference. Whether the inhibitory effect of intrahippocampal injection of L-NAME is the result of the NO-induced regulation of the blood–brain barrier permeability to morphine may be considered. The present data suggest that the NO pathway in the CA1 area of the rat hippocampus could be involved in conditioned place preference.

In the present study, the effects of L-arginine and L-NAME on the expression of morphine-induced conditioned place preference were also studied. The pretest administration of L-arginine, but not L-NAME, increased the expression of morphine-induced conditioned place preference. When L-NAME was injected into the hippocampal CA1 area, 1 min before the injection of L-arginine, the response to L-arginine was blocked, the mechanism of which is not clear.

It has been found that the NMDA receptor antagonist MK-801 attenuates the development of opiate tolerance and dependence in rats (Trujillo and Akil, 1991; Marek et al., 1991). It has also been observed that some central effects of NMDA receptors are likely to be mediated via the activation of NOS, with a subsequent release of NO (Snyder and Bredt, 1991; Bredt and Snyder, 1992). Moreover, the activation of NMDA receptors in the central nervous system results in an increase in the activity of NOS (Garthwaite, 1991), thereby supporting the involvement of the NO system in the behavioral effects induced by morphine. These findings suggest the possibility that L-arginine increases the NOS activity induced most probably by the activation of the NMDA receptors, which, in turn, modulates the effects of morphine.

The hippocampus receives a dopaminergic projection originating predominantly in the ventral tegmental area (Scatton et al., 1980). Evidence demonstrates a transmitter role for dopamine in the hippocampus (Bischoff, 1986). The dopaminergic system is also involved in reward (Robinson and Becker, 1986; Bardo, 1998; McBride et al., 1999). Furthermore, the dopaminergic actions of cocaine and also cocaine-induced reverse tolerance and conditioned place preference may be mediated partially via the activation of the NO system (Kim and Park, 1995). Packard and White (1991) also indicated that the dopaminergic system is involved in modulating the memory processes of the hippocampus. Evidence also suggests that NO is a retrograde transmitter that signals presynaptic neurons, causing an increase in the release of dopamine (Pudiak and Bozarth, 1993). Therefore, NO may be a neuronal messenger mediating the release of dopamine in the CA1 area of the rat hippocampus, which could explain the enhanced morphine-induced conditioned place preference, observed in these experiments.

It has been proposed that damage to the dorsal hippocampus interferes with spatial learning (Ferbinteanu and McDonald, 2001). As conditioned place preference is a learning paradigm, in that animals must remember the place and cues associated with drug administration (Olmstead and Franklin, 1997a), the present study indicates that the NO system might play a role in mediating this type of learning. In summary, this study examined the possible role of the NO system in the CA1 area of the rat hippocampus on the acquisition and expression of conditioned place preference induced by morphine, and showed that the conditioned rewarding effect (conditioned place preference) of morphine was enhanced in animals injected with the NO precursor, L-arginine. The NO system in the rat hippocampal CA1 area, therefore, may be involved in morphine-induced conditioned place preference.

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